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EDITORIAL

Pegylated Interferon Lambda and Ramatroban as Host-Directed Countermeasures for Future Respiratory Viral Pandemics: A Position Paper

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Abstract

Future respiratory viral pandemics will require deployable countermeasures before pathogen-specific vaccines and direct antivirals become available. Host-directed therapies may offer broader activity across respiratory viruses and greater resilience to viral evolution. Pegylated interferon lambda (pegIFN-ë), a type III interferon with epithelial-predominant antiviral activity, and ramatroban, an antagonist of thromboxane A2/prostaglandin D2 signaling, have both been proposed as pandemic-agnostic interventions. Current evidence supports a stronger case for pegIFN-ë than for ramatroban. PegIFN-ë has randomized outpatient efficacy data in COVID-19 and a biologic rationale aligned with early respiratory epithelial infection [1,2]. Ramatroban has mechanistic plausibility and repurposing appeal but lacks robust clinical efficacy data in viral respiratory disease [3,4]. Neither agent can currently be expected to terminate outbreaks or prevent pandemics as a standalone intervention [5,6]. A rational preparedness strategy would prioritize pegIFN-ë for protocolized early-use evaluation and stockpiling assessment, while positioning ramatroban within adaptive repurposing trials [7,8].

Keywords:

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Introduction

Pandemic preparedness has historically depended too heavily on pathogen-specific countermeasures that arrive after widespread transmission is already established [8-10]. The COVID-19 pandemic illustrated this vulnerability: effective vaccines required approximately one year of development, and direct-acting antivirals such as nirmatrelvir/ritonavir reached clinical use even later. During the intervening period, the global community relied on non-pharmaceutical interventions, repurposed drugs of uncertain efficacy, and supportive care.

This recurring gap has renewed interest in broad-acting and host-directed antivirals that could be deployed early, before a new respiratory pathogen is fully characterized [7,11,12]. Host-directed therapies target conserved cellular pathways exploited by diverse viruses, potentially offering activity that is less vulnerable to viral mutation and more readily transferable across pathogen families.

This position paper evaluates two host-directed candidates — pegylated interferon lambda and ramatroban — and proposes a tiered preparedness framework based on the current strength of evidence for each.

Pegylated Interferon Lambda

Biologic rationale

Type III interferons (IFN-ë1–4) signal through a heterodimeric receptor complex (IFNLR1/IL-10Râ) whose expression is largely restricted to epithelial cells at barrier surfaces, including the respiratory, gastrointestinal, and hepatic epithelia [2,13,14]. This restricted receptor distribution enables IFN-ë to induce potent antiviral gene programs at the site of initial respiratory viral infection while producing less systemic immune activation than type I interferons. The kinetics of IFN-ë signaling are also distinct, with a slower onset but more sustained antiviral state that may be particularly suited to early intervention [13-14].

This biology is directly relevant to pandemic preparedness because most respiratory viruses — including influenza, coronaviruses, respiratory syncytial virus, and parainfluenza viruses — establish

initial infection in the airway epithelium, precisely where IFN-ë exerts its dominant effects.

Clinical evidence in COVID-19

PegIFN-ë is among the few host-targeted agents to have demonstrated efficacy in a randomized phase 3 trial during a respiratory pandemic. In the TOGETHER trial, 1,951 high-risk outpatients with COVID-19 were randomized to a single 180 ìg subcutaneous injection of pegIFN-ë or placebo within 7 days of symptom onset. The primary composite outcome of hospitalization or prolonged emergency department observation (>6 hours) occurred in 2.7% of the pegIFN-ë group versus 5.6% of the placebo group (relative risk 0.49; 95% Bayesian credible interval 0.30–0.76) [1].

Subgroup analyses suggested that benefit was greatest among patients treated within 3 days of symptom onset and among those with higher baseline viral loads, consistent with the mechanistic expectation that early intervention at the epithelial level would be most effective before systemic disease is established [1,2]. Effects were broadly consistent across SARS-CoV-2 variants and vaccination strata [1].

Earlier phase 2 data from Feld et al. demonstrated accelerated viral clearance with pegIFN-ë, particularly among patients with baseline viral loads above 10v copies/mL [2]. A separate phase 2 trial by Jagannathan et al. did not meet its primary endpoint, though differences in patient population and timing of treatment may account for the discrepancy [15]. Santer et al. reported that pegIFN-ë accelerated SARS-CoV-2 clearance even in older adults with delayed adaptive immune responses [16].

Preclinical breadth

Evidence from preclinical investigations indicates that IFN-ë exerts antiviral activity against MERS-CoV in animal models and demonstrates inhibitory effects against multiple RNA viruses, including influenza, under laboratory conditions [17-18]. While these observations support its potential as a broad-spectrum respiratory antiviral therapy, further clinical studies are required to confirm its efficacy across diverse viral infections in humans.

Safety profile

Clinical development programs evaluating pegIFN-ë for hepatitis B, C, and D have generally demonstrated a more favorable tolerability profile compared with pegIFN-á, with lower incidences of flu-like symptoms, hematological toxicities, and neuropsychiatric adverse effects [19-22]. Nevertheless, abnormalities in liver function tests have been reported consistently across studies. Elevations in serum transaminases and bilirubin levels, the latter potentially related to the inhibition of organic anion-transporting polypeptides, have been documented and, in some cases, necessitated discontinuation of therapy [20,23,24]. Although the single-dose regimen used in the TOGETHER trial was reported to be well tolerated, wider clinical implementation would warrant careful monitoring of hepatic function to ensure patient safety [1].

Ramatroban

Biologic rationale

Ramatroban is a dual antagonist of the thromboxane A, (TP) and prostaglandin D, (DP2/CRTH2) receptors, both of which are involved in the pathogenesis of severe viral respiratory infections [3,4,25,26]. By inhibiting these pathways, it may reduce thrombotic, inflammatory, and immune-mediated complications associated with severe disease [25,26]. The drug is orally active and has been used in Japan for allergic rhinitis since 2000, with a well-established safety profile [4,27].

Evidence limitations

Despite its strong mechanistic rationale, current clinical evidence supporting the use of ramatroban in viral respiratory infections remains limited. Human data are restricted to a small uncontrolled case series involving four patients with COVID-19 pneumonia, and no randomized controlled trials have assessed its efficacy for prevention, treatment, or reduction of transmission in respiratory viral diseases [3,4]. Furthermore, the complex nature of prostanoid signaling necessitates careful interpretation, as modulation of these pathways may produce variable effects depending on the biological context, with some studies suggesting the potential for enhanced immunopathology [28,29]. Consequently, although ramatroban shows therapeutic promise, robust clinical trials are required before its widespread use can be recommended.

Can These Therapies Terminate Outbreaks or Prevent Pandemics?

The potential of host-directed therapies to control outbreaks or prevent pandemics is a key consideration in pandemic preparedness. However, current evidence is insufficient to support such a role for either pegIFN-ë or ramatroban. Effective outbreak control through therapeutic interventions requires early administration, large-scale accessibility, an acceptable safety profile, and the ability to significantly reduce transmission.[5,6] Experience with influenza antivirals has shown that although early treatment may decrease transmission within households and communities, its impact is highly dependent on timing, coverage, and epidemiological circumstances [5,6,30–32]. Moreover, antiviral therapy alone has generally been inadequate to halt widespread transmission once an epidemic becomes established [6,9,10]. For pegIFN-ë, evidence regarding reduction of viral transmission is lacking, as clinical studies have primarily focused on patient outcomes rather than transmission dynamics [1]. In the case of ramatroban, conclusions regarding outbreak control remain speculative due to the absence of robust efficacy data [3,4]. Therefore, while these agents may help lessen disease severity, lower viral burden, and potentially contribute to transmission reduction, they should be viewed as complementary measures rather than substitutes for established public health strategies such as surveillance, diagnostic testing, isolation measures, and vaccination programs [5,8,9]. Based on the current evidence, a rational preparedness strategy should position these agents in distinct tiers.

Operational integration

Effective use of these therapies during future outbreaks requires integration into a coordinated preparedness framework. Key components include predefined emergency activation criteria, rapid diagnostic testing for early case detection, continuous pharmacovigilance for safety monitoring, alignment with emerging virus-specific interventions, and clear communication regarding their investigational status, benefits, and limitations.

Preparedness Tier	Therapeutic Candidate	Strategic Objective	Key Preparedness Actions
Tier 1	**Pegylated Interferon Lambda (pegIFN-λ)**	**Priority investigational countermeasure with potential for early outbreak mitigation**	• Establish regulatory readiness through early engagement with health authorities to avail emergency-use pathways. • Assessment of manufacturing capacity, supply-chain resilience, and feasibility of stockpiling. • Development of adaptive clinical trial platforms that can be rapidly implemented during the emerging outbreaks. • Pre-define treatment path emphasizing administration during the early symptomatic phase (preferably within 72 hours of symptom onset). • Design protocols for hepatic function evaluation and ongoing safety monitoring parameters. • Prioritize research areas assessing post-exposure prophylaxis, transmission reduction, and effectiveness in high-risk or closed-population settings.
Tier 2	**Ramatroban**	**Repurposing candidate requiring rapid clinical evaluation**	• Include ramatroban within pre-established adaptive platform trial networks for rapid evaluation during outbreaks. • Focus initial assessments on patients exhibiting early respiratory compromise, hypoxemia, or evidence of thrombo-inflammatory activation. • Restrict its role to investigational use only until availability of robust randomized clinical trial evidence. • Support translational and mechanistic studies to identify optimal patient populations and disease stages most likely to benefit.

Conclusion

Host-directed therapies may play an important supportive role in future respiratory pandemic preparedness, but their present evidence base warrants cautious interpretation. PegIFN-ë has emerged as the more advanced agent, supported by a plausible biological mechanism and encouraging clinical data, whereas ramatroban remains an investigational option requiring further evaluation. At present, neither therapy can be considered a standalone solution for outbreak control or pandemic prevention. Future outbreak preparedness efforts should focus on strengthening clinical trial readiness, regulatory planning, manufacturing capacity, and integration of these agents with established public health measures. With continued research and validation, these therapies could become valuable components of a comprehensive early-response strategy against emerging respiratory viral threats.

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