Peginterferon Lambda for the treatment COVID-19

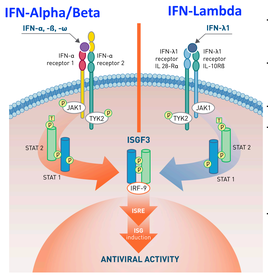
TORONTO CENTRE FOR LIVER DISEASE

C Kandel*[1], MJ Biondi*[1,2], R. Kozak[1], MA Zahoor[1,2], I Choong[3], C Hislop[3], J Glenn[4], AJ Gehring[1,2], HLA Janssen[1,2], B Hansen[1,2], JJ Feld[1,2].

1. University of Toronto. 2. Toronto Centre for Liver Disease, 3. Eiger Biopharmaceuticals 4. Stanford School of Medicine.
* Contributed equally to the work

UHN Toronto General Hospital

Background



Type I Systemic vs Type III Epithelial

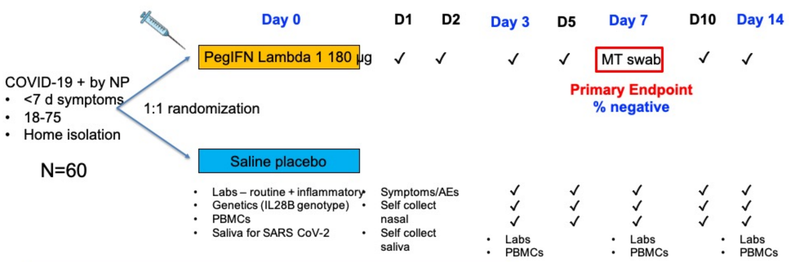
- Interferons (IFN) are a major component of the innate antiviral immune response and produced in response to viral infection
- Interferons drive induction of a host of genes with antiviral and immunoregulatory properties known as interferon stimulated genes
- Interferons are divided based on the receptor used for signaling
- The Type I interferon receptor (alpha/beta) is expressed on every cell in the body whereas the Type III interferon receptor (lambda) is expressed primarily in epithelial tissues: lung, liver, intestine with limited expression on inflammatory cells
- Interferon lambda has been shown to be important in controlling respiratory viral infections (eg. influenza) with a lower chance of stimulating a systemic response such as cytokine storm syndrome
- Interferon lambda induction is impaired in COVID-19 but interferon lambda treatment suppresses SARS-CoV-2 in cell culture and animal models
- Peginterferon lambda has been used in >3000 patients with HBV and HCV infections with similar antiviral activity but better side effect profile than interferon alpha

We therefore hypothesized that treatment with interferon lambda would be effective for treatment of mild to moderate COVID-19

Aims

A phase II randomized, double blind, placebo-controlled, multicenter trial to evaluate the effect of peginterferon lambda for the treatment of COVID-19

Methods



Pre-specified analysis of primary endpoint controlling for baseline viral load

Inclusion Criteria:
- 18-75 yo
- within 7 d of symptom onset or first + swab if asymptomatic

Exclusion Criteria:
- Need for hospital admission
- Immunosuppression
- Pregnancy
- Medical conditions potentially worsened by PegIFN lambda – seizure disorder, autoimmune disease, active retinal disease, severe psychiatric disease
- Other significant comorbidity that would preclude use of PegIFN lambda

Statistical analysis
- ITT analysis – missing counted as positive
- Proportion positive at Day 7 (crude and controlled for baseline viral load)
- Factors associated with clearance by logistic regression

Laboratory Analysis
- Quantitative PCR for SARS-CoV-2 using plasmid-derived cDNA standards
- Anti-SARS-Co-V2 antibodies – IgG - Diasorin

Results

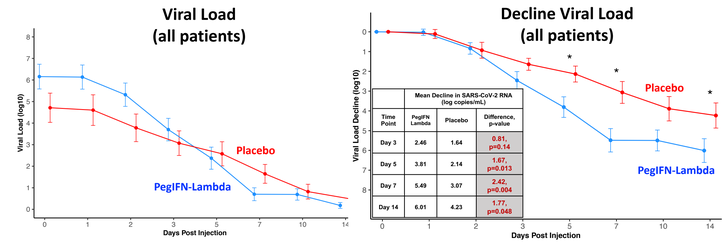
Table 1. Patient Demographic and Disease Characteristics

		IFN Lambda (n=30)	Placebo (n=30)
Sex	Male	12 (40%)	13 (43%)
	Female	18 (60%)	17 (57%)
Age	Years (SD)	44 (13)	42 (13)
Race	White	15 (50%)	16 (53%)
	Black	1 (3%)	5 (15%)
	Asian	8 (27%)	7 (23%)
	Other	6 (18%)	2 (6%)
Co-morbidity	DM/CHF/HTN	5 (17%)	4 (13%)
BMI	Mean (SD)	27.3 (5.2)	26.1 (4.2)
BMI Category	<25	9 (30%)	11 (37%)
	25-30	15 (50%)	13 (43%)
	>30	6 (20%)	6 (20%)
IFNL4 genotype	Non-TT	18 (60%)	16 (57%)
	TT	12 (40%	12 (43%)

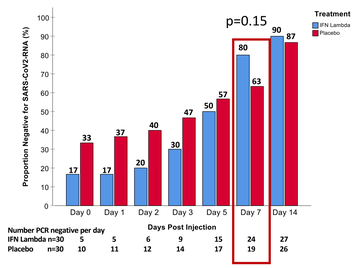
		IFN Lambda (n=30)	Placebo (n=30)
Duration of Symptoms	Days, Mean (SD)	4.3 (1.7)	4.7 (1.7)
Time from test to Day 0	Days, Mean (SD)	3.2 (1.1)	3.3 (1.2)
Asymptomatic		5 (18%)	6 (21%)

	IFN Lambda (n=30)	Placebo (n=30)
Viral load baseline, mean (SD) log copies/mL	6.2 (3.1)	4.9 (3.7)
Viral load undetectable at BL, n(%)	5 (17%)	10 (33%)
Viral load >10E6 copies/mL, n(%)	19 (63%)	16 (53%)
Anti-SARS CO-V2 IgG S + at Day 0	0/27 (0%)	5/24 (21%)

Figure 2. Mean SARS-CoV-2 viral load over time and mean decline viral load



The mean decline in viral load was greater with peginterferon lambda treatment than control started at Day 3, with a maximal difference of 2.42 log copies/mL greater than placebo at Day 7 post-dosing.



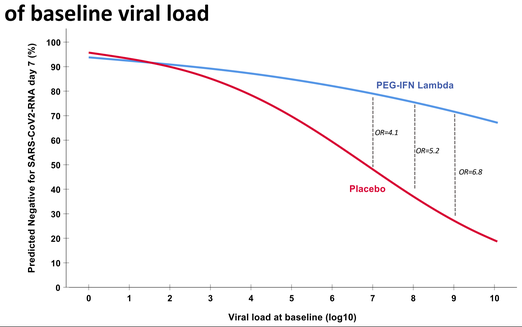
Baseline viral load strongly associated with probability of clearance at Day 7 – OR 0.64 (0.40-0.85, p=0.0009)

Controlling for baseline viral load:

	Odds Ratio (95% CI)
PegIFN Lambda vs Placebo	4.12 (1.15-16.7), p=0.029
Viral load at baseline	0.69 (0.51-0.87), p=0.001

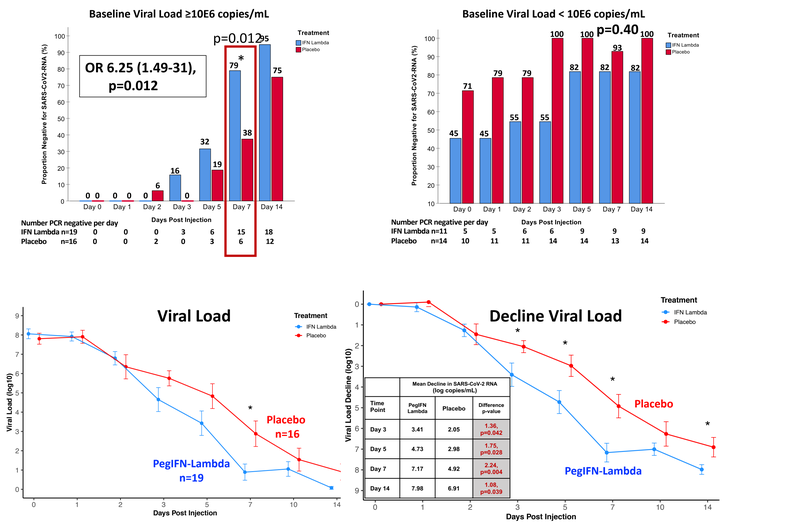
Baseline viral load was strongly associated with clearance by Day 7. After controlling for baseline viral load, peginterferon lambda treatment was associated with clearance by Day 7 (primary endpoint).

Figure 3. Probability of clearance with peginterferon lambda vs placebo as a function of baseline viral load



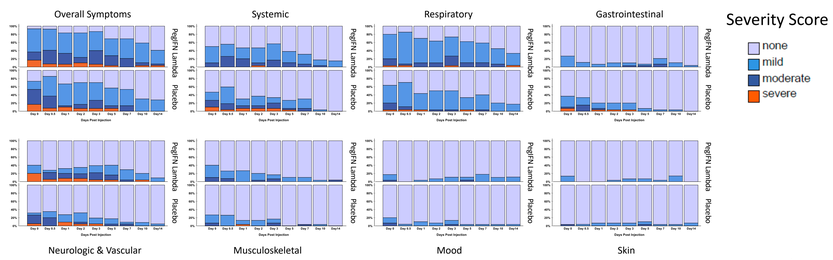
At low baseline viral load, clearance by Day 7 is likely in both groups. With every log increase in baseline viral load, the odds of clearance by Day 7 with peginterferon lambda vs placebo increases.

Figure 4. Proportion negative at Day 7 and mean viral load and decline in viral load stratified by baseline VL above or below 6 log copies/mL



In those with a high baseline viral load (>10E6 copies/mL), the probability of clearance by Day 7 and viral load decline was greater in those treated with peginterferon lambda than placebo. No difference was seen in those with low viral load, with rapid clearance in both groups

Figure 5. Symptoms improved in both groups over time



Symptoms improved over time in both groups with a trend toward more rapid improvement in respiratory symptoms with peginterferon lambda treatment (p=0.06). Transient aminotransferase elevations were more common with peginterferon lambda than placebo: no other safety signals observed

Conclusions

- Peginterferon lambda treatment accelerated viral decline in outpatients with mild to moderate COVID-19.
- Antiviral effects were most pronounced in those with high baseline viral loads
- Treatment led to increased clearance within 1 week of dosing
- Peginterferon lambda was well tolerated with a similar side effect profile to placebo and only mild transient liver enzyme elevations
- Rapid reduction of viral load in the outpatient setting may:
  - Prevent progression in the individual
  - Reduce transmission
  - Shorten the duration of required self-isolation

Future Directions

- Evaluation of peginterferon lambda treatment in hospitalized patients and ambulatory patients at high risk of severe COVID-19

Acknowledgements

COVID-19 ACTION FUND DONATE TODAY

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- Ontario Together

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