Safety, tolerability and biological activity of repeated intranasal administration of TLR3 agonist Ampligen (Poly I:Poly C12U) in healthy subjects

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Introduction

Rintatolimod (Ampligen®), a synthetic double-stranded RNA (Poly I:Poly C12U), is a Toll-like receptor 3 (TLR3) agonist, inducing type-I interferons. Intranasal administration of rintatolimod could induce an innate mucosal immune response, thereby inhibiting respiratory viruses at the point of entry. Rintatolimod could have potential as a prophylactic or early treatment against respiratory viral infections. Here we present data of a phase I trial investigating a repeated dosing regimen of intranasal rintatolimod.

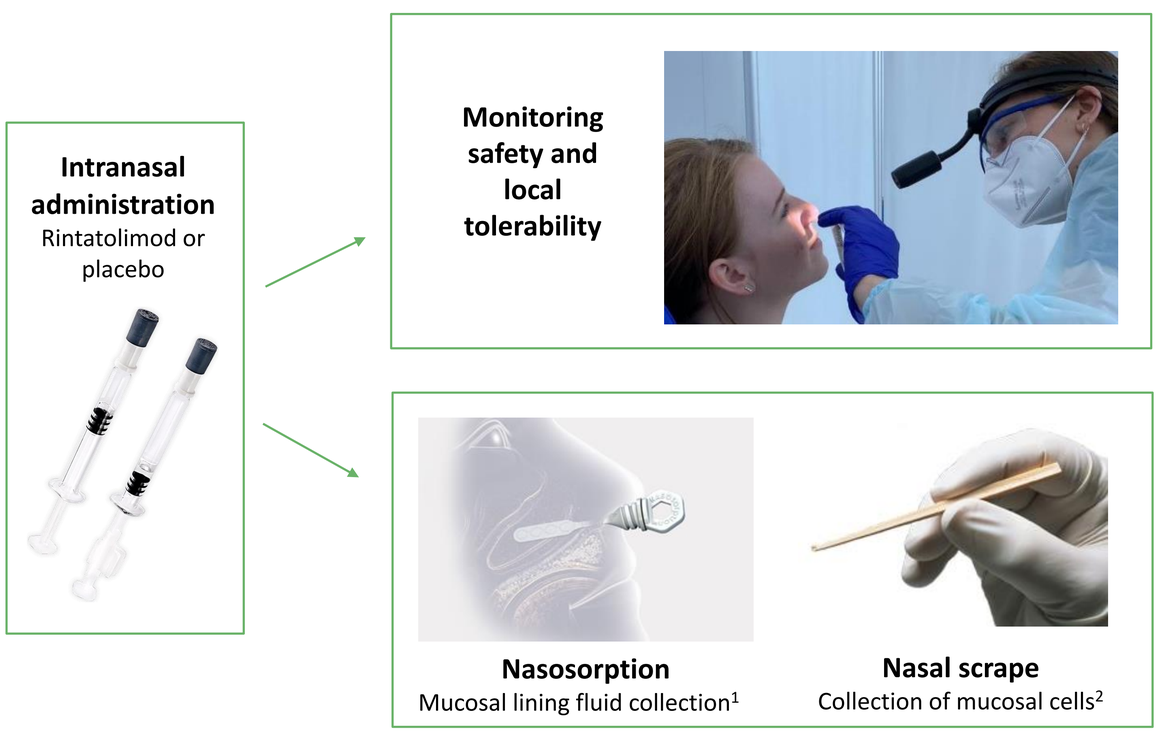
Aim

To assess the safety, tolerability and biological activity of a 13-day dosing regimen for intranasal rintatolimod administered every other day

Methods

Study design (figure 1)

- Randomized, double blind, dose-escalation study
- 7 consecutive intranasal doses of rintatolimod or placebo administered every other day
- Study population: healthy male and female subjects (age 18-70 yrs)
- Four cohorts of 10 subjects (8 active: 2 placebo)
- Dose levels: 75ug, 200ug, 500ug, 1250ug.



	D1			D2	D3	D5	D7	D9	D11	D13			D14	D15
	0h	3h	6h							0h	3h	6h		
Intranasal administration	x				x	x	x	x	x	x				
Nasosorption[1]	x		x	x	x		x		x	x		x	x	x
Nasal scrape[2]	x	x	x	x	x		x		x	x	x	x	x	x

[1] Type I interferons (IFN-α, IFN-β), NFκB-mediated cytokines (IFN-γ, IL-6, IL-8, TNF), chemokines (CXCL10, RANTES, MCP-1) were measured in mucosal lining fluid.
[2] Mucosal immune cell were characterized by flow cytometry (granulocytes, T cells, B cells, dendritic cells, NK cells, monocytes)

Figure 1: Study design

Results

- Repeated intranasal administration of rintatolimod was well tolerated. No severe or serious AEs reported.
- Solicited local AEs were comparable across all treatment groups and placebo.
- An increase in IL-6, IL-8, and TNF production was observed for both rintatolimod and placebo after dosing.
- MCP-1 and RANTES peaked 3-24 hours after administration, mainly for 500 µg rintatolimod (figure 2&3)
- At doses evaluated, intranasal rintatolimod administration did not drive a significant change in nasal immune cell abundance.

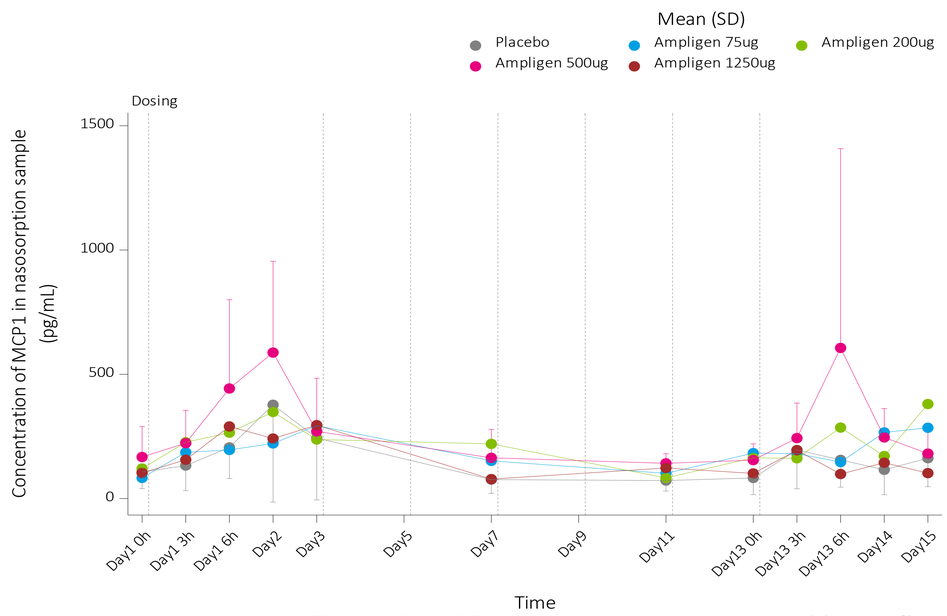


Figure 2: MCP1 concentration in mucosal lining fluid

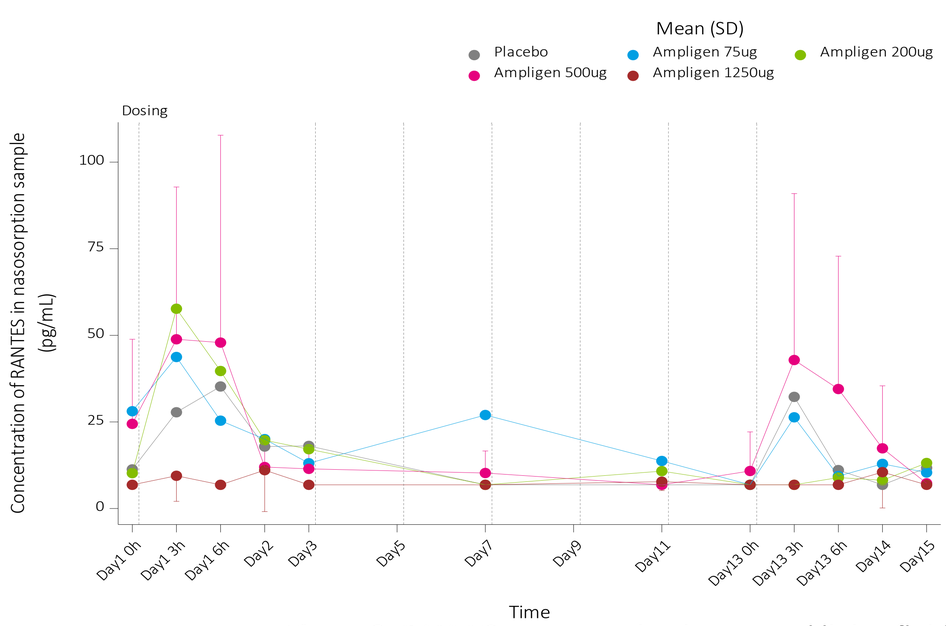


Figure 3: RANTES concentration in mucosal lining fluid

Conclusions

- Repeated intranasal administration of rintatolimod every other day was well tolerated in all tested dose levels.
- No significant change in cytokine or chemokine production in the nasal lining fluid after rintatolimod treatment. However, for MCP-1 and RANTES, increases were observed mainly at 500 µg dose level.

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