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Antiviral Polymers - A Novel Concept for Prophylactic and Therapeutic Interventions

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Summary:

While science and societies are struggling to find ways to protect humankind from recurring epidemics and pandemics of influenza, cheap and readily available prophylactic and therapeutic options are still needed.

Here we introduce the concept of creating a protective physical barrier in the nasal cavity with an antiviral polymer (Carrageenan)[1-3] that works as inhibitor against virus entry for prophylaxis and therapy of influenza.

Independent clinical trials in adults and children revealed that the intranasal administration of iota-Carrageenan significantly reduced the time to disease clearance of patients with common cold and decreased the virus load in nasal lavages. This was also true for a subgroup of patients infected with influenza A virus.

In addition, a combination of Carrageenan with the NA inhibitors Oseltamivir[2] or Zanamivir showed superior results in lethal influenza infection mouse models when compared with each compound alone. Thus, we suggest the combination of Carrageenan and Zanamivir in a nasal spray as novel concept for prophylactic and therapeutic intervention against influenza virus infection.

Carrageenan

Figure 1. Iota-Carrageenan is marketed in Austria as the active component of the nasal spray Coldamaris Prophylactic®.

Carrageenan is a **sulfated polymer** derived from red seaweed that has been extensively used in the food, cosmetic and pharmaceutical industry and has been generally recognized as safe by the FDA (**GRAS**).

The intranasal application of Carrageenan creates a **protective physical barrier** in the nasal cavity and works as inhibitor against virus entry.

Clinical Study Design

Pooled analysis of two clinical trials conducted with similar design: randomized, parallel group, double blind and placebo-controlled studies in therapeutic natural setting with **common cold** infected patients experiencing symptoms ≤48 hours

Therapy: 3x / day application of the Carrageenan containing nasal spray

1. Children´s trial in St. Anna hospital, Vienna[4]
   213 patients enrolled, >1 year, average age 4 years
2. Adult´s trial in Vienna
   220 patients enrolled, >18 years, average age 33.5 years

Broad Anti-Viral Effectiveness of Carrageenan

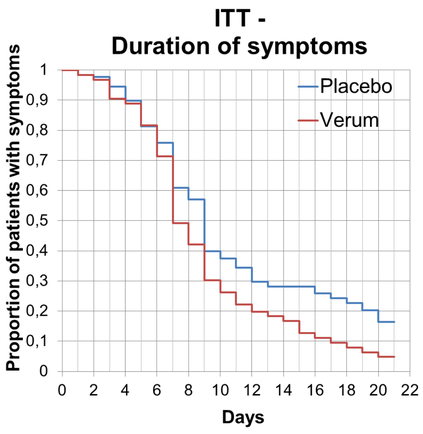


Figure 2. Significantly **shorter** duration of disease compared to placebo (**1.9 days** in ITT, p=0.002)

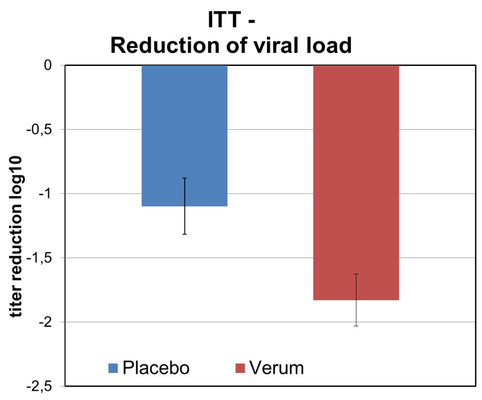


Figure 3. Significant **reduction of viral load** in nasal secretions (ITT, p=0.015)

ITT … Intention To Treat population

Anti-Influenza A Effectiveness of Carrageenan

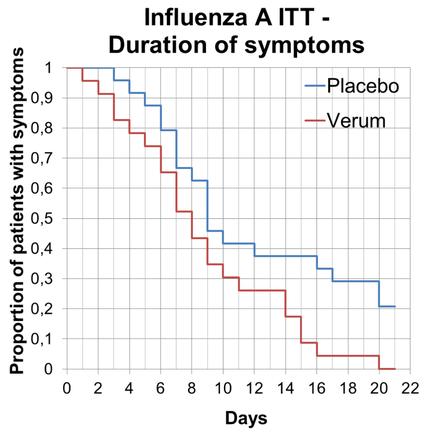


Figure 4. Significantly **shorter** duration of disease compared to placebo (**3.3 days** in ITT, p=0.002)

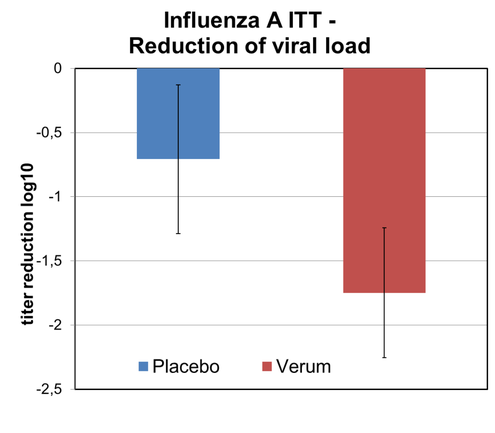


Figure 5. Significant **reduction of influenza virus load** in nasal secretions (ITT, p=0.002)

ITT … Intention To Treat population

Combination of Carrageenan and Zanamivir - Advantages

- Combination of 2 **clinically proven** marketed products

Clinical Evaluation	Carrageenan	Zanamivir
Clinical effectiveness of intranasal application	468 patients	297 patients
Safety evaluation of intranasal application	> 400,000 units sold	1496 patients

- **Nasal application** of the combination product
- Suitable for **children** <5 years
- Two different mechanism of action
  → Reduced risk of escape mutants
- Both products **reduce viral load** in the nasal cavity
- Both products **shorten** the duration of viral **disease**
- Broad antiviral effectiveness of Carrageenan
  → Additional treatment of concomitant viruses

Combination – Proof of Concept

Figure 6. I*n-vivo* experiment set-up

The infectious dose of **A/PR/8/34 (H1N1)** 6.3×10^3 PFU and the treatment start (**48 hours post infection**) was determined to get a set up that shows minimum activity of both components tested alone.

This same set-up was used to test the single components in combination.

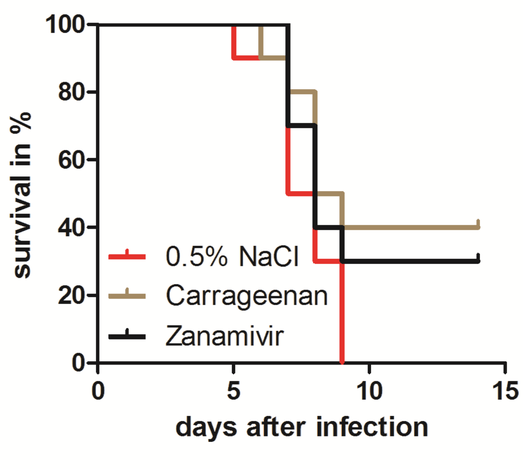
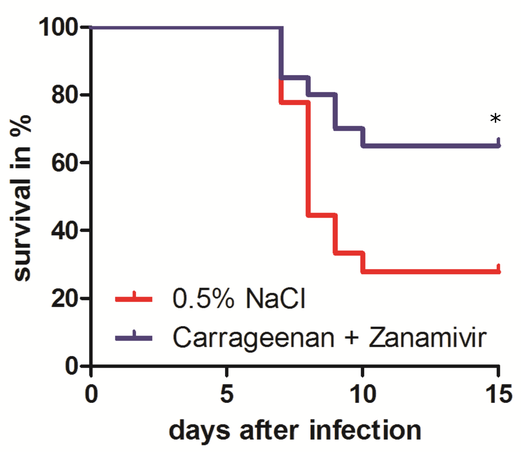


Figure 7. I*n-vivo* efficacy of the Combination

Ten mice per group were intranasally infected with 6.3×10^3 PFU A/PR/8/34 (H1N1) viral particles at day 0.

Intranasal therapy started 48 hours post infection twice daily with 240 µg Carrageenan in 0.5% NaCl plus 0.5 mg/kg/day Zanamivir (blue) or 0.5% NaCl as Placebo (red).

* Wilcoxon test p=0.0221



Conclusion

Data from clinical studies demonstrate that Carrageenan containing nasal spray is effective against respiratory viruses. Patients experienced reduced duration of common cold symptoms and faster elimination of viruses from nasal cavities.

Based on the superior efficacy results of the combination of Carrageenan and Zanamivir in animals, we suggest a clinical trial for prevention or treatment of influenza A in humans.

Because alternatives to Oseltamivir are desperately needed, we propose the nasal spray containing Carrageenan and Zanamivir as an option for treatment of influenza.

References:

1. Grassauer A, et al. (2008) Iota-Carrageenan is a potent inhibitor of rhinovirus infection, Virology Journal.
2. Leibbrandt A, et al. (2010) Iota-Carrageenan Is a Potent Inhibitor of Influenza A Virus Infection. PLoS ONE
3. Eccles R, et al. (2010) Efficacy and safety of an antiviral Iota-Carrageenan nasal spray: a randomized, double-blind, placebo controlled pilot study in volunteers with early symptoms of the common cold, Respiratory Research
4. Fazekas T, et al. (2012) Lessons learned from a double-blind randomised placebo-controlled study with a iota-carrageenan nasal spray as medical device in children with acute symptoms of common cold, BMC Complementary and Alternative Medicine 2012.