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Combination of a corticosteroid and an anti-viral intranasal therapy

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Background:

Intranasal corticosteroids (INCS) provide potent, localized treatment for allergic rhinitis (AR), idiopathic rhinitis, rhinosinusitis and nasal polyposis with minimal risk of systemic exposure. However, corticosteroids cause immunosuppression and can decrease the anatomical barrier function of the skin. Consequently, infection and multiplication of all types of pathogens (bacteria, viruses and fungi) may occur, while alleviating inflammation.

Viral infections of the upper respiratory tract are known to increase the hyperreactivity to allergens in AR patients and play an important role in asthma development and asthma decompensation.[1,2] In general, allergens and viruses may act together to exacerbate asthma. Consequently, strategies to reduce the impact of asthma exacerbations should include interventions directed to both, suppression of viruses and reducing allergen exposure.[3]

Following the request for alternative therapies to modulate viral pathogenesis[4] and for treatment of upper airways diseases to reduce the risk of development of asthma[5], we suggest the combination of INCS with a broad anti-viral therapy.

Here we introduce the concept of creating a protective physical barrier in the nasal cavity with an antiviral polymer (iota-carrageenan) that works as inhibitor against respiratory virus entry for prophylaxis and therapy.[6] 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.[7,8] Iota-carrageenan is already marketed in Europe as antiviral active component of medical device nasal sprays under different brand names.

Iota-Carrageenan

Figure 1. Iota-carrageenan is marketed in 13 countries as the active component of an anti-viral nasal spray (in Austria under the brand name 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 iota-carrageenan containing nasal spray

1. Children´s trial in St. Anna hospital, Vienna[8]
   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 Iota-Carrageenan

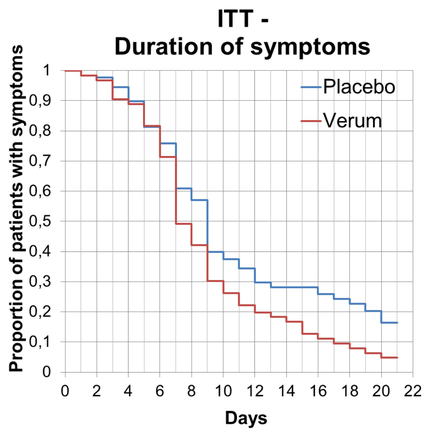


Figure 2. Significantly **shorter** duration of disease compared to placebo (**1.9 days** in ITT, p=0.002)

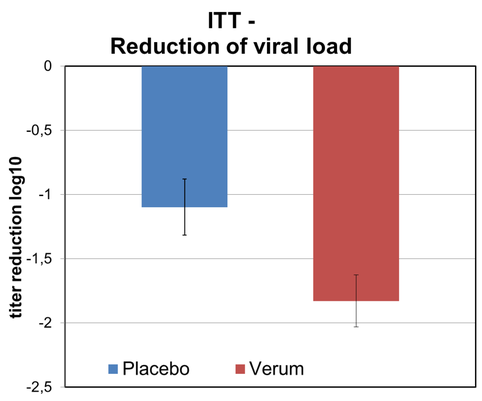


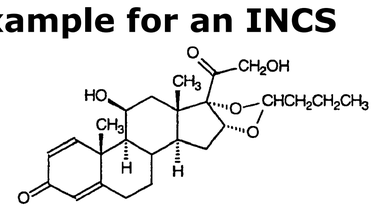
Figure 3. Significant **reduction of viral load** in nasal secretions (ITT, p=0.015)

ITT … Intention To Treat population

Budesonide – example for an INCS

Figure 4. Chemical structure of budesonide

Well established corticosteroid with long-term experience for intranasal application. Clinically safe and effective in adults and children.



Combination – Proof of Concept

Figure 5. The **anti-inflammatory** property of budesonide present in the **combination** was shown by inhibition of LPS induced TNF-alpha in murine whole blood.

Budesonide in the combination with iota-carrageenan resulted in the **same inhibition** of LPS induced TNF-alpha **as Budesonide alone**.

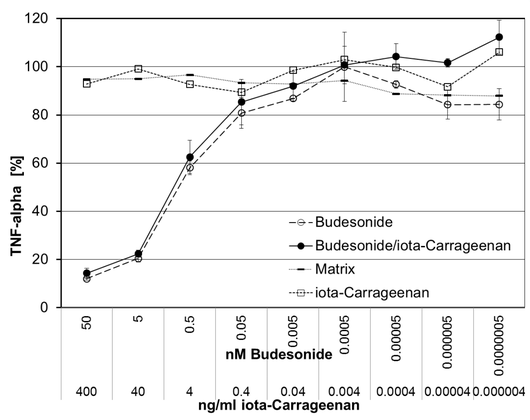
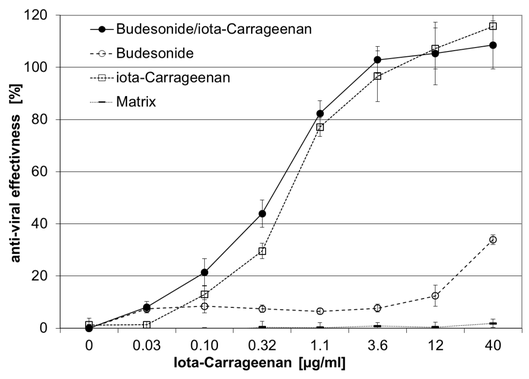


Figure 6. The **anti-viral** efficacy of iota-carrageenan against **human rhinovirus** (HRV8) was evaluated by inhibition of virus replication induced cell death on HeLa cells.

The inhibition of human rhinovirus by iota-carrageenan **was not influenced** by the **combination** with budesonide.



Formulations	Combination	Iota-Carrageenan	Budesonide
human coronavirus (OC43)	0.024 µg/ml	0.024 µg/ml	no inhibition
influenza A (H1N1(pdm)09)	0.8 µg/ml	0.8 µg/ml	no inhibition

Table 1. The **anti-viral** efficacy of iota-carrageenan against **influenza virus** and **human coronavirus** was evaluated by inhibition of virus induced haemagglutination of erythrocytes. The obtained lowest concentration of iota-carrageenan required for complete inhibition of haemagglutination was **not influenced** by the **combination** with budesonide.

Summary

We suggest the combination of an intranasal applicable corticosteroid, using as example budesonide - a well described corticosteroid with a long history of use as intranasal drug, with iota-carrageenan in a nasal spray.

A combined formulation of budesonide and iota-carrageenan was tested in-vitro for its anti-inflammatory activity and anti-viral effectiveness against human rhinovirus, influenza virus and human coronavirus.

Both substances – budesonide and iota-carrageenan - showed irrespective of their combination an unmodified action in-vitro.

Thus, patients would benefit from a fast treatment of symptoms of rhinitis together with an efficient anti-viral prophylaxis and treatment.

References:

1. Calhoun et al., J. Clin. Invest., 1994
2. Lemanske et al., J. Clin. Invest., 1989
3. Murray et al., Proc Am Thorac Soc., 2004
4. Jackson et al., J Allergy Clin Immunol, 2011
5. WHO, 2003
6. Grassauer A, et al., Virology Journal, 2008
7. Eccles R, et al., Respiratory Research, 2010
8. Fazekas T, et al., BMC Complementary and Alternative Medicine, 2012

In relation to this presentation, I declare the following, real or perceived conflicts of interest: employment with the presenting company