

Licensing Opportunity



UCA derivatives: a new family of small molecular anti-inflammatory drug candidate compounds

- Proven anti-inflammatory effects in models in vivo and in vitro
- Very good safety profile
- Wide range of possible clinical indications

Therapy | Immune suppressive agents | dermatology | auto immune diseases

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Background

When the upper skin is exposed to UVB radiation from the sun or other sources, anti-inflammatory effects will occur. One particular cause is the formation of cis-urocanic acid (cis-UCA) from trans-UCA by a process of photoisomerization.

We discovered that oxidation of UCA by UVB radiation or other factors will also lead to compounds with anti-inflammatory properties.

The Technology

We have identified the so-called UCA oxidation products (UOPs see patent 1) and shown the anti-inflammatory properties of 3 compounds in several tests. Moreover, we designed and patented a large class of lipophilic UCA derivatives enhancing the skin penetration (patent 2). Anti-inflammatory effects of two ethyl esters of this large group were studied.

Several tests in vitro indicated effects that fit in an anti-inflammatory pattern. Immunoscreen studies had been performed for the two original UOPs and suppression of CCR1 and CCR5 expression was found, among others.

UCA derivatives stimulated IL10 levels in LPS-triggered whole blood and some interaction with H2-receptors became apparent.

One UCA derivative showed substantial suppression of extracellular ROS-production, by triggered granulocytes, which finding led to the focus on acne.

UCA derivatives suppressed IL-6 and TNF- α levels and stimulated IL-10 from triggered monocytes in culture (Fig. 1), which effects indicate anti-inflammatory behaviour.

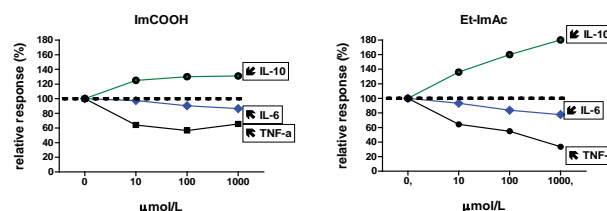


Figure 1. Effect of two UCA derivatives, ImCOOH and an esterified UCA derivative, on cytokine-levels of TNF- α , IL-6 and IL-10. Cytokine levels without test compounds were set to 100 %

Preclinical tests (safety efficacy)

Out of the first group of products 3 UOPs were tested for their tox profile in preclinical tests. Two showed a good safety profile. ImCOOH, was taken into the clinical test phase I, as a topical agent in a cream.

Topical application of ImCOOH showed good immunosuppression in several in vitro and in vivo tests. Mouse studies were performed for the suppression of allergic contact dermatitis (ACD) by the UCA-derivatives. Mouse ear swelling was induced by a contact sensitizer and topically applied UCA derivatives were studied for reduction of that swelling (Fig. 2).

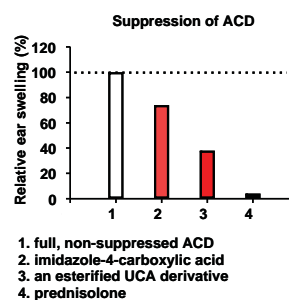


Figure 2. Suppression of allergic contact dermatitis (ACD) by UCA derivatives and prednisolone. The full, non-suppressed ear swelling was set to 100 %.

Recently, UCA derivatives were studied for their usefulness in inflamed bowel disease (IBD). Intraperitoneal administration was performed in an experimental colitis mouse model. To that end, an experimental colitis mouse model and an ex-vivo model were used. Several results were consistent with an anti-IBD behavior.

Clinical study (safety efficacy)

The excellent safety profile was confirmed in healthy subjects (phase I study), in mild atopic dermatitis patients (n=30) and acne patients (n=10). Besides safety also efficacy was studied in the patient studies.

Applications

Dermatological indications: atopic dermatitis (AD) and acne were studied in the first place, later on followed by IBD in vitro and an animal model (results of first tests are positive). However, the drugs might also have a place in other autoimmune diseases like psoriasis.

R&D Status

One natural occurring UCA derivative was taken into clinical test phase I and IIa for AD and acne. A backup compound is available (preclinical safety tests showed a good profile). Other indications with these compounds should be tested further.

From the large group of synthetic UCA derivatives, two ethyl esters were subject to several preclinical test in vitro and in vivo, also revealing a good safety and efficacy profile.

Intellectual Property

Patent 1: US7056938 (B1); EP1196129 (B1); and granted in other countries Priority date: 1999-06-25

Patent 2 : WO2008NL50367 Priority date: 2007-06-11

Patent 3: WO2011028112 Priority date: 2009-09-02

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Key publications

1. Kammeyer A, Eggelte TA, Overmars H, Bootsma A, Bos JD, Teunissen MBM, Oxidative breakdown and conversion of UCA isomers by hydroxyl radical generating systems, *Biochim Biophys Acta* 1526 (2001) 277 - 285.
2. Kammeyer A, Bos JD and Teunissen MBM, Postelicitation model of allergic contact dermatitis for predicting the efficacy of topical drugs, *Exp. Dermatol.* 18 (2009) 44 - 49