IMO-8400, a novel TLR7, TLR8 and TLR9 antagonist, inhibits disease development in mouse models of psoriasis

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Introduction

Toll-like Receptors (TLRs) 7, 8 and 9 can recognize endogenous immune complexes containing self-RNA and -DNA, respectively. In many autoimmune diseases, TLR7- and 9-mediated inflammation induced by immune complexes leads to maintenance and progression of disease.

Activation of TLR7, TLR8 and TLR9 in pDC and mDC through the interaction of these receptors with the antimicrobial peptide LL37 complexed with self-RNA or DNA contributes to psoriasis development\(^1,2\). Therefore, inhibition of TLRs 7, 8 and 9 through the use of a TLR antagonist could provide therapeutic effect in this autoimmune disease.

We have identified a first-in-class DNA-based antagonist of TLR7, 8, and 9, referred to as IMO-8400. IMO-8400 inhibits TLR7- and 9-mediated immune responses in mice and TLR7-, 8- and 9-mediated immune responses in human cell-based assays and in non-human primates.

In the present study, we have evaluated IMO-8400 as a therapeutic agent in IL-23- and LL-37-induced psoriasis models in mice.

Role of TLRs 7, 8 and 9 in Psoriasis: Induction of IL-23 and IL-17 Pathways

Protein-RNA/DNA complex

TLR7/9

pDC

IFN-α

IMO-8400

TLRs 7, 8 and 9 antagonist

CD11c+ DC

TLR8

IL-20

activation

B-Defensin

S100A7

IL-8

IL-23

IL-17

IL-22

Th17

Th1

activation

IFN-γ

TNF-α

KC

IP-10

MIG

IL-12

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Outline of Study Protocol of IL-23-Induced Psoriasis

Female C57BL/6 mice, 6 weeks old

Experimental groups (n = 8/group)
IMO-8400, 300 μg/dose (15 mg/kg)
PBS
Naïve

Evaluation
Skin histology
Gene expression in skin
Treatment with IMO-8400 Suppresses Skin Lesions Induced by IL-23

IL-23 induced various degrees of erythema and induration. IMO-8400 inhibited inflammation induced by IL-23.
Treatment with IMO-8400 Inhibits Skin Inflammation Induced by IL-23

Naive  
PBS-treated  
IMO-8400-treated

Epidermal hyperplasia  
Inflammatory cell infiltration  
Abscess  
HE stain, Magnification x 200
Expression of S100 and β-defensin (DEFB4) genes is up-regulated in lesions of psoriasis patients; IMO-8400 significantly suppressed expression of both genes. Gene expression was determined by quantitative real-time PCR.
Treatment with IMO-8400 Reduces IL-17 and Increases IL-10 Levels in IL-23-Injected Skin

* P < 0.05 vs PBS group. Cytokine levels were determined by ELISA
Splenocytes From IMO-8400-Treated Mice Show Reduced Response to TLR9 Agonist Stimulation

*P < 0.05 vs PBS. Cytokine levels were determined by ELISA.
Outline of Study Protocol of LL-37-Induced Psoriasis

Female C57BL/6 mice, 8 weeks old

**Experimental groups (n = 7/group)**
- IMO-8400, 50 μg/dose (2.5 mg/kg)
- IMO-8400, 100 μg/dose (5 mg/kg)
- IMO-8400, 300 μg/dose (15 mg/kg)
- PBS
- Naïve

**LL-37, 50 μg, i.d. at root of ear once every two days**

**IMO-8400, s.c. once every two days**

**Termination**

**Evaluation**
- Ear thickness
- Skin histology
Treatment with IMO-8400 Suppresses Ear Thickness Increase Induced by LL-37

* P < 0.05 vs. PBS group
Treatment with IMO-8400 Reduces Skin Inflammation Induced by LL-37

Naive

PBS

IMO-8400, 300 µg

Epidermal hyperplasia

Inflammatory cell infiltration

HE stain, Magnification x 100
Summary

- IMO-8400 is a first-in-class antagonist of TLR7, 8 and 9

- In IL-23-induced psoriasis model, IMO-8400 suppressed
  - Psoriatic lesions, epidermal hyperplasia and inflammatory cell infiltration
  - DEFB4 and S100A gene expression and IL-17 protein levels
  - TLR9-mediated immune responses in splenocytes

- IMO-8400 treatment increased IL-10 gene expression and protein levels in skin

- In LL-37-induced psoriasis model, IMO-8400 reduced
  - Ear thickness, epidermal hyperplasia and inflammatory cell infiltration

- IMO-8400 is in development for treatment of autoimmune diseases