Toll-like Receptor Antagonism as a Novel Anti-inflammatory Treatment Approach for Duchenne Muscular Dystrophy

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BACKGROUND

- Duchenne muscular dystrophy (DMD) is a progressive and fatal muscle disease with limited treatment options.
- While DMD is caused by a defect in the dystrophin gene, immunologic and inflammatory processes play a central role in driving skeletal and cardiac muscle weakness and failure.
- Anti-inflammatory corticosteroids are the standard of care, but significant adverse effects have been observed with chronic use in children.

- Toll-like receptors (TLRs) are key components of the innate immune system, and are involved in regulating inflammation and adaptive immunity.
- TLR antagonism represents a novel treatment approach for DMD with the potential to suppress muscle inflammation and thereby slow disease progression.

- IMO-8400 is a novel oligonucleotide-based antagonist of endosomal TLRs 7, 8 and 9.
- IMO-8400 was generally well tolerated in a Phase 1 clinical trial in healthy volunteers.
- IMO-8400 was generally well tolerated and demonstrated evidence of clinical activity in a Phase 2 clinical trial in patients with psoasias, an immune-mediated inflammatory disease in which TLRs are implicated.

- Here we review preclinical evidence that support the initiation of clinical development of IMO-8400 as a potential non-steroidal anti-inflammatory treatment for DMD.

DISCUSSION

TLRs play a critical role in the disease pathogenesis of DMD

- Dystrophin-deficient muscle cells are damaged due to contraction injury and release self-DNA, self-RNA and other nucleic acid products, activating innate immunity.
- DAMPs activate TLRs, which initiate inflammation, leading to activation of pro-inflammatory cytokines and T cell activation.
- Increased immune activity and inflammation cause muscle cell death, ultimately triggering a vicious cycle.

Knockout of the MYD88 gene in mdx mice demonstrates the role of the TLR pathway in DMD

- MYD88 antagonists are effective in reducing muscle inflammation and improving muscle function in mdx mice.
- Inhibition of the TLR pathway in the mdx mouse model significantly improved muscle strength and function.
- In addition, significant improvements in markers of immune activation were observed.

Dose-dependent increase in muscle function

- Treatment with IMO-8400 resulted in a dose-dependent increase in muscle function.
- Significant improvements in specific force of the extensor digitorum longus (EDL) muscle were observed.

Decrease in pro-inflammatory cytokine gene expression

- Plasma creatine kinase levels were significantly decreased in high dose groups.
- Specific force of the EDL muscle was improved in high dose groups.
- Inflammatory cytokine gene expression, markers of muscle damage and immune activation, were also significantly decreased in high dose groups.

CONCLUSIONS

- Toll-like receptor antagonism represents a non-steroidal anti-inflammatory therapeutic approach applicable to all patients with DMD regardless of dystrophin genotype.
- TLRs are key drivers of muscle inflammation and are over-activated in DMD patients at all stages of the disease.
- Improved skeletal and cardiac muscle function was observed in 1-year-old mdx mice with double MYD88 knockout, demonstrating the role of the TLR pathway in the disease process.
- The investigational TLR antagonist improved muscle inflammation, cytokine gene expression, markers of muscle damage and immune activation, and EDL muscle function following five weeks of treatment in mdx mice.
- Collectively, these data support advancing IMO-8400, an investigational antagonist of TLRs 7, 8 and 9, into clinical development for the treatment of DMD patients.

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