Research corner

Novel NLRP3 targeted therapy in CAPS

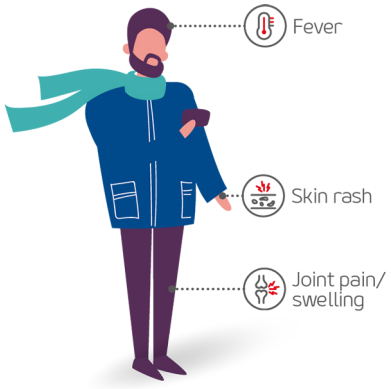
Source: Presentation by Hal M. Hoffman at ISSAID 2019

Therapies against Cryopirin-associated periodic syndrome usually rely on IL-1ß inhibitors. Improved knowledge on the role of the NLRP3 inflammasome is paving the way for the development of alternative options to improve patient care.

Moving from the sole IL-1 target to expand the list of potential therapeutic options

Cryopyrin-associated periodic syndrome (CAPS) is a group of rare, heterogeneous autoinflammatory disease. Skin and joint involvement being accompanied by IL-1ß-mediated systemic inflammation, the currently used therapies involve IL-1ß inhibitors: rilonacept (arcalist) and canakinumab (ilaris). Anakinra, targeting IL-1 receptor, is another option.

Improved understanding of the underlying mechanisms revealed that the *ca.* 90 different mutations identified in *NLRP3* can lead to activation of the cryopyrin inflammasome and inappropriate release of inflammatory cytokines including IL-1ß. Triggering the pathways that are important for the normal regulation of the NLRP3 inflammasome is thus a promising way for preventing CAPS-related uncontrolled inflammation.



Main clinical features of CAPS

NLRP3 inhibitors to strengthen the armamentarium

MCC950/CRID3 is an old potent and selective inhibitor of the NLRP3 inflammasome pathway. Four companies started to look into developing better forms of this drug to potentially have less side effects. However recent results suggest that MCC950/CRID3-based therapies may not effectively treat inflammation driven by CAPS-associated mutants.

The novel NLRP3 inhibitor C1 is also being investigated. Preclinical results highlight its ability to significantly reduce LPS (lipopolysaccharides) induced IL-1ß release both in cells from CAPS patients and in murine NLRP3 mutant models. These results suggest direct and effective inhibition of mutant NLRP3 activation. Moreover, daily oral administration of C1 was well tolerated and showed efficacy in preventing weight loss, splenomegaly, leucocytosis, and liver inflammation in mice (MWS NLRP3/+CreT inducible mice).

C1 and other emerging NLRP3 inhibitors present an additional avenue for future CAPS patient therapy by directly targeting the inflammasome.

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