

## **NITRIC OXIDE (NO)-DONATING GLUCOCORTICOIDS SHOW PHARMACOLOGICAL PROPERTIES WHICH TRANSLATE INTO CLINICAL BENEFITS**

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NO-donating glucocorticoids represent a novel class of compounds which share similar potency with glucocorticoids, but display additional benefits. Here we present data of one prototype, NCX 1015.

Like prednisolone, NCX 1015 potently and dose-dependently reduced clinical score and all inflammatory parameters in a murine model of collagen-induced arthritis (CIA). The activity was confirmed in a carrageenan-induced air-pouch inflammation. NCX 1015 and prednisolone both reduced infiltrating leukocytes, as well as PGE<sub>2</sub>, LTB<sub>4</sub> and nitrite levels in pouch exudates; however, a higher dose of prednisolone was necessary to produce comparable effects to NCX 1015. NCX 1015 protected mice from 2,4,6-trinitrobenzene sulfonic acid induced-colitis by modulating T helper cell type 1 (Th1)-mediated healing. This effect was reflected by improvement in macroscopic and histological score of the colon mucosa, reduction of Th1-derived cytokines, diminished myeloperoxidase activity, and increased animal survival rate. Also here in general, NCX 1015 was more potent than prednisolone e.g., in inhibiting IFN- $\gamma$  secretion by mononuclear cells infiltrating the lamina propria. The capacity of NCX 1015 to potently stimulate *in vivo* IL-10 production, suggested that its activity can be partially ascribed to the induction of a regulatory subset of T cells that negatively modulates inflammation. NCX 1015 also effectively improved the recovery of function in a murine model of spinal cord injury by reducing apoptosis of spinal cells, effect not shared by prednisolone.

NCX 1015 brought about safety benefits on cardiovascular and bone metabolism side effects. In the CIA model, prednisolone, but not NCX 1015, showed increase in blood pyridinoline, a bone and cartilage erosion marker, and elevates bone resorption activity in rat primary osteoclasts *in vitro*. Unlike prednisolone, NCX 1015 did not affect endothelin system and did not show blood pressure increase. These results show that NCX 1015 possesses enhanced activity and tolerability in comparison with prednisolone. While NCX 1015 is being further evaluated, other NO-donating glucocorticoids are being currently developed for specific clinical indications, such as asthma and dermatological disorders.