The S100A9 inhibitor paquinimod reduces synovial activation, osteophyte formation and cartilage damage in experimental osteoarthritis.

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Disclosure

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Introduction – Methods – Results – Conclusions

S100A8/S100A9

• Damage Associated Molecular Pattern (DAMP) or “alarmins”, implicated in various inflammatory diseases (SLE, MS, CF, RA)
  • Produced by neutrophils, monocytes, activated macrophages
  • S100A8, S100A9 stimulate (OA) chondrocytes to produce cytokines and MMPs
  • Described receptors TLR4, RAGE

S100A8/S100A9

• S100A9-/- reduced synovial activation, cartilage damage in collagenase induced OA (model with high synovial activation)
  • S100A9-/- mice show reduced osteophyte size in collagenase induced OA (poster #46)

Treatment options OA

• Treatment options for OA limited; focused on symptoms
  • Blocking S100A8 or S100A9 could be an interesting therapeutic option for inhibiting joint destruction in osteoarthritis (with synovial involvement)
Paquinimod (ABR-215757)

- Quinoline-3-carboxamide derivate
- Strong binding to S100A9, blocking interaction S100A9-TLR4 / S100A9-RAGE
- Disease inhibition in several disease models, including systemic sclerosis (SSc) and experimental lupus model, well tolerated by SLE & SSc patients

To investigate the effect of inhibiting S100A9 by paquinimod on joint pathology during experimental OA

Objective

Experimental OA models

- Two models of experimental OA, differing in the level of synovial activation
  - Collagenase induced OA (CIOA) - HIGH SYNOVIAL ACTIVATION
  - Destabilization of the medial meniscus (DMM) - low synovial activation

Paquinimod has only minor effects on joint destruction in DMM OA model

Cartilage damage (modified Pritzker OARSI score)
Osteophyte size
Paquinimod reduces synovial activation in collagenase induced OA

Paquinimod reduces osteophyte size in collagenase induced OA

Paquinimod reduces cartilage damage in collagenase induced OA

Paquinimod reduces synovial activation in collagenase induced OA

Paquinimod reduces osteophyte size in collagenase induced OA

Paquinimod reduces cartilage damage in collagenase induced OA
Paquinimod can be administered in the drinking water of mice without affecting body weight.

Blocking of S100A9 by paquinimod treatment reduces synovial activation, cartilage damage & osteophyte size on day 42 of collagenase induced OA.

Blocking of S100A9 by paquinimod treatment in DMM only reduces cartilage damage at one location and does not influence osteophyte size.

Blocking of S100A9 by paquinimod inhibits joint pathology in experimental OA with substantial synovial activation.

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