Methods: OA patients were treated with CS (800 mg/day) or paracetamol (4 g/day) for 6 month. Clinical examination was performed at baseline, and after 1.5, 6 and 9 months of treatment, with collection of plasma and synovial fluid. The clinical examination included measurement of the overflow, hypertrophy and vascularisation of the synovia as well as functional study of the articulation (with Lequesne and EVA index). The levels of CXCL1, fractalkine/CX3CL1, MCP-1/CC-2, RANTES/CC5 and GRO-/CXCL1 were determined by ELISA in the plasma and synovial samples collected. The statistical analysis was performed with SPSS package. We performed two different analyses. In the first one, we studied the difference between the levels of the chemokine between each time and the baseline. We performed this analysis in separate with the paracetamol group and chondroitin one. For this comparison we used a non parametric test (Wilcoxon 2 related samples test). We performed a second analysis in order to analyze if there were differences in the chemokine levels over time, depending on the treatment received. For this analysis an independent sample t-test was performed.

Results: Improvements in the clinical signs of inflammation were detected after 6-9 months after CS treatment of OA patients. The comparison of the levels of each chemokine at the different times studied versus the baseline, indicated us that these effects were accompanied by a significant reduction in the synovial levels of MCP-1 at 6 month (p=0.05), whereas in the paracetamol group there was a significant increased level of RANTES (p=0.035). In plasma, only MCP-1 concentration was significant diminished (p=0.023) by CS administration. To study in global the answer to the treatments, we perform a comparison between the effect of each drug to the levels of each chemokine. This analysis showed us that there were significant differences between the response to the treatment in MCP-1, 6 month after treatment (p=0.016), and in fractalkine, 9 month after treatment (p=0.036). In both cases the treatment with chondroitin showed a diminution of the levels of the chemokines, while paracetamol didn't affect in the case of MCP-1 or even increased in the case of fractalkine. All these data show that the chemokine attraction of macrophage. T-cell, eosinophil and basophil is reduced with a 6 month treatment with chondroitin.

Conclusions: These results suggest that CS sulphate may represent an adequate drug to reduce the inflammation associated to the OA process.

579

LINKING AN ADAMTS5-SPECIFIC THERAPEUTIC MONOCLONAL ANTIBODY TO A SENSITIVE BIOCHEMICAL MARKER OF TARGET ENGAGEMENT AND ACTIVITY FOR POTENTIAL APPLICATION AS A COMPANION DIAGNOSTIC

J. Larkin, GlaxoSmithKline, King of Prussia, PA, USA

Purpose: The goal of co-developing a companion diagnostic alongside a therapeutic has distinct advantages for drug development and has recently been suggested by some regulatory agencies to be the preferred scenario for future approvals. The ability to identify patient subsets most likely to respond to and benefit from a treatment not only allows for focused stratification and reduced development costs, but also has the potential to reduce healthcare expenditures through defined treatment guidelines. This scenario is especially useful in the context of osteoarthritis (OA) where the sheer patient numbers, multifactorial etiology and unmet need of the patient population dictates an effective stratified approach to clinical development and market acceptance.

Methods: The Target: ADAMTS5 - A Disintegrin And Metalloprotease with Thrombospondin motifs 5, is a key protease involved in degradation of cartilage (aggrecan). Activity is upregulated in osteoarthritis, and inflammatory arthritis leads to impaired joint function and disability. Genetic loss of function is associated with cartilage protection in preclinical disease models.

The Therapeutic: A high affinity humanized mAb that specifically binds and neutralizes ADAMTS5, engages the target in vivo (cartilage), inhibits cartilage degradation with extended duration in human OA cartilage explant studies, and dose dependently modulates circulating ARGS neo-epitope levels following systemic administration in cynomolgus monkeys, supporting its potential as an OA disease modifying drug.

Results: The Diagnostic: ARGS Neoepitope - A sensitive immunosassay capable of quantifying a specific ‘signature’ of ADAMTS5-mediated cleavage of aggrecan in serum, plasma, urine and synovial fluid with applications for patient selection, monitoring response and potentially efficacy.

Conclusions: The Therapeutic Profile: By delaying structural disease progression, and stabilizing or improving pain and/or function, it will fill a large unmet need in joint diseases. As a chronic therapy, the safety profile will be suitable for long term administration.

580

THE ESSENTIAL OIL OF ERYNGIUM DURIAEI SUBSP. JURESIUM INHIBITS IL-1β INDUCED NF-KB AND MAPK ACTIVATION IN HUMAN CHONDROCYTES

A.T. Rufino 1,2, C. Cavalheiro 3, F. Judas 4, L. Salgueiro 3, M.C. Lopes 1,2, A.F. Mendes 1,2, 1 Ctr. for NeuroSci. and Cell Biology, Coimbra, Portugal; 2 Faculty of Pharmacy, Univ. of Coimbra, Coimbra, Portugal; 3 Lab. of Pharmacognosy, Faculty of Pharmacy/CEF, Univ. of Coimbra, Coimbra, Portugal; 4 Univ. Hosp. of Coimbra and Faculty of Med. of Univ. of Coimbra, Coimbra, Portugal

Purpose: Intracellular signaling pathways, including NF-kB and mitogen-activated protein kinases (MAPK), modulated by pro-inflammatory cytokines, like IL-1β, are known to regulate several genes involved in the inflammatory and catabolic processes that lead to cartilage degradation. Therefore, these signaling intermediates are considered promising targets for the development of anti-osteoarthritic drugs with potential disease modifying properties. Essential oils are complex mixtures of low molecular weight lipophilic molecules with favorable pharmacokinetic properties that make them especially suited collections for drug screening. Our previous studies showed that the essential oil isolated from the aerial parts of Eryngium duriae subsp. juresiunum (M. Lainz) M. Lainz (an Apiaceae species endemic in the Iberian Peninsula) reduced IL-1β-induced iNOS expression and nitric oxide production. This work aimed at further elucidating the mechanism of action of that essential oil in human chondrocytes, as part of a strategy to identify natural compounds with potential disease modifying anti-osteoarthritic activity.

Methods: Knee cartilage samples (n=5) were obtained from multi-organ donors (23 to 67 years old, mean=43.2) at the University Hospital of Coimbra with approval by the Ethics Committee. After enzymatic digestion, cells were plated and cultured under non-proliferating conditions. C28/I2 chondrocytic cells were used in some experiments. Cells were serum starved for 8 to 24 h and treated with 3 different concentrations of essential oil solutions in DMSO for 30 min before stimulation with IL-1β, 10 ng/mL, for 5 or 30 min. The protein levels of total and phosphorylated IkBα, and phosphorylated p38, JNK and ERK1/2 MAPK were assessed by western blot.

Results: In a concentration of 0.02% (v/v), the essential oil significantly decreased IL-1β-induced phosphorylation of IkBα, JNK, p38 and ERK1/2 by 78.0±3.9%, 55.6±6.7%, 36.4±6.0% and 244±3.3%, respectively (p<0.001). Even in a concentration nearly 10 fold lower (0.0025% v/v), the essential oil still inhibited JNK and p38 phosphorylation by 21.9±4.48% and 23.1±6.11%, respectively (p<0.05).

Conclusions: These results show that the essential oil of E. duriae subsp. juresiunum reduces both IL-1- and NF-kB and MAPK activation, although it is more effective towards inhibition of NF-kB and JNK. Taken together, the results obtained suggest that this essential oil contains compound(s) that may present anti-inflammatory and anti-catabolic properties, and thus, potential disease-modifying anti-osteoarthritic activity. Future work will focus on the fractionation and identification of those compounds followed by further pharmacologic characterization.

Therapy – Surgical & Intraarticular

581

10 YEAR SURVIVORSHIP OF THE MEDIAL OXFORD UNICOMPARTMENTAL KNEE ARTHROPLASTY. A 1000 PATIENT NON-DESIGNER SERIES - THE EFFECT OF SURGICAL GRADE AND SUPERVISION.


Purpose: The Oxford Unicompartmental Knee Arthroplasty (OUKA) is a well established treatment option for anteromedial gonarthrosis. The