Results and conclusions: We will also explore how these guidelines, recommendations and points to consider can lead the way to value based healthcare in the future.

I-17
BIOLOGICAL AGENTS IN OA - HOPES AND DISAPPOINTMENTS

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Purpose: To review the trial in humans using biologics in osteoarthritis (OA) which can be can be categorized according to the main target: pain, structure or both.
Methods: A literature review (Medline, Cochrane, Embase) of the most recent trials in OA using biologics
Results: The analgesic effect of anti-nerve growth factor (NGF) was initially dramatic using high dose and intravenous route of administration, but emerging severe arthropathies (in the targeted knee but not only) have dampened down this enthusiasm. Most recent trials used anti NGF Mab, administered subcutaneously, with lower dose, shorter interval of administration and without concomitant use of NSAIDS. The effect on pain is still superior to placebo but with a much lesser magnitude. Unfortunately, long term follow-up in those trials still shows a concern in terms safety profile. Thus, Patients who will benefit of this anti NGF therapy should be strictly selected and followed up. Biologics agents targeting main cytokines (interleukines 1 and 6, tumor necrosis alpha) have been tested in knee OA and in hand OA. The first randomized controled trial in humans using a single local administration of the antagonist of IL-1, at 2 doses: 50 and 150 mg, failed to show an analgesic effect, except at day 3 with the highest dose. This negative result has been confirmed in trials using systemic administration of monoclonal antibodies directed against only IL1-β or against IL-1 α and Il-1 β in patients with knee OA and in patients with hand OA. However, in the CANTOR trial recruiting patients with cardiovascular disease treated with canakinumab, post hoc analysis indicated that the patients in the verum group, shows a dramatic decrease in the number of total joint replacement (hip and knee) (about 50%). This might open a door for a possible anti IL-1 strategy dedicated to patients with some part of systemic inflammation. Most of trial with anti TNF inhibitors have been performed in patients with erosive digital hand OA and all were negative on pain and on structure (measured by different parameters on magnetic resonance imaging). Finally the last cytokine that has been targeted is IL-6. Results of the RCP trial in hand OA are ongoing. Taking all together, biologics in OA are really disappointing, raising more questions than answers: choice of the targets, choice of selected phenotype of pain, selection of the route of administration, too short time of intra articular residence of the drug etc. News biologics targeting WNT, bradykinin or anti sense micro RNA are under development but so far, the preliminary results needs to be confirmed in large trials in humans. Finally, the last option is to try to stimulate the cartilage repair response which is naturally weak. Fibroblast growth factor 18 (sprifremin), an anabolic and mitogenic factor for the chondrocyte, has been tested against placebo in an ambitious trial over 5 years with 2 years of treatment and 3 years of follow-up. The drug was intra-articularly delivered every 6 months or every 12 months, with 2 different dosages. At the first end point, at year 2, with the highest dose of FGF-18, a statistically significant difference with the placebo was observed on the cartilage volume measured by MRI in the global, medial and lateral compartment on the involved knee. Unfortunately, there was no effect on pain in the ITT population, except in a sub group of patients with a minimum threshold of pain and an initial joint space width between 1.5mm and 3.5 mm (around one third of the population) show a significant effect on pain reduction compared to placebo. If results of this long term trial are confirmed in others trials, FGF-18 may constitute the first real disease modifying drug in OA. Conclusions
Conclusion: The trials in humans using biologics are disappointing. We should keep in mind that blocking a single mediator will not stop the catabolic process in OA. Thus in the next future, we should probably adapt a drug owing to the evolution of the disease, to the profile of patient, to the radiological aspect of the disease and to the phenotype of pain. The story is just starting ……

I-18
THE ROLE OF SYNOVIUM IN THE ONSET AND PROGRESSION OF OA

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Conventionally, the synovial changes in OA are considered to be a secondary event associated with cartilage degeneration. However, recent studies have shown that synovial changes are actively involved in the pathology of OA. This presentation provides an overview of our current understanding of the synovial changes in knee OA. Clinically, the significance of synovial changes in OA is two-fold. First, synovial changes are closely related to the symptoms of knee OA, especially pain. Studies using MRI have revealed that the presence of effusion-synovitis in knee joints is associated with knee pain. Second, synovial changes may be related to the structural progression of knee OA. The results of cohort studies have consistently indicated that knees with effusion-synovitis are at higher risk for disease progression. Thus, synovial changes may play a pivotal role in the pathology of OA by causing pain and cartilage degeneration. The severity of synovial changes in OA joints may change with time. This may explain some of the clinical features of OA. For example, the symptoms of knee OA may fluctuate with time, and the progression of OA is often phasic. These features may be related to the vacillation of synovial changes. Synovial changes may occur irrespective of the severity of structural changes observed on radiographs. Again, this may explain the dissociation between the extent of structural changes and the severity of symptoms which is often encountered with the disease. While most of the above findings were obtained from observations of established OA, recent studies have focused on the knee joints in the very early stage of the disease, or early OA, in an attempt to elucidate the initial change(s) that may trigger the disease. The results of such studies have shown that the synovial changes may occur prior to the development of radiographic changes, and that such changes may cause pain and structural changes in the joints of early OA patients, as occurs in established OA. Thus, synovial changes may be an initial event of OA, which plays a key role in the initiation of the disease. Despite its significance, the mechanism(s) underlying synovial changes in OA has not yet been elucidated. Again, it is not known why synovial changes are related to pain or structural progression. It is therefore necessary to elucidate the mechanism(s) underlying the synovial change in OA since it will be helpful to establish effective treatments for knee OA.