Selective COX-2 Inhibitors

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1. Introduction

Knee osteoarthritis (OA) is a condition that leads to pain and is mainly characterized by cartilage degradation [1]. Currently, drug treatments provide symptomatic pain relief but no effective treatment exists to slow down progression of OA-related cartilage damage [1]. Pain-killing drug therapies include non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs provide pain relief by blocking cyclooxygenase (COX)-dependent prostanoid synthesis. Prostanoids are an important family of signaling molecules present in synovial fluid [2]. At least two COX isoforms have been described, COX-1 and COX-2, the latter being considered as the inflammatory isoform [3]. Selective COX-2 inhibitors have been developed to specifically target the inflammatory COX-2 while circumventing inhibition of the COX-1 isoform. While selective COX-2 inhibitors may provide an effective means for pain relief, targeting the inflammatory COX-2 may be also a promising approach to inhibit cartilage degradation and thereby slow down knee OA progression [3]. This hypothesis is supported by the accumulating evidence showing that inflammation precedes OA disease progression [3][4].

From the anti-nerve growth factor clinical trials it became clear that next to a substantial improvement in pain, patients also displayed structural OA disease progression [5]. This emphasizes the importance of treatment strategies not only providing pain relief, which will lead to a vicious self-perpetuating cycle of joint overloading and OA progression, but also providing the ability for disease modification.

The actions of non-selective COX inhibitors on cartilage degradation in vitro and in vivo have been excellently reviewed in the past [6]. Moreover, ex vivo and in vivo actions of the selective COX-2 inhibitor celecoxib on cartilage degradation, synovial inflammation and osteoclast metabolism have also been reviewed and date back to 2011 [7]. Recently, an updated review of studies published until 2016 has been conducted on the OA disease-modifying actions of celecoxib on different OA tissues. This review confirms the contradictive reports regarding the chondroprotective actions of celecoxib both ex vivo and in vivo. Based on these reviews, it still remains obscure whether selective COX-2 inhibitors can be used in vivo to protect cartilage and slow down the progression of knee OA. One of the explanations of the contradictive reports found in the literature regarding the potential of selective COX-2 inhibitors may be related to the route of administration. Specifically, scarcely vascularized tissues such as cartilage and meniscus, which are important participants in knee OA, may be modified differentially after systemic oral treatment compared to intra-articular treatment [8][9]. To date, the role of the route of administration on the chondroprotective effects of selective COX-2 inhibitors remains unclear.

2. Discussion

The main finding of this systematic review is that the administration route plays a major role in determining chondroprotective actions of selective COX-2 inhibitors. The intra-articular administration route may be promising, since studies using bolus intra-articular administration of selective COX-2 inhibitors show chondroprotective effects. On the other hand, conflicting evidence exists when selective COX-2 inhibitors are incorporated into a drug delivery system. While preclinical studies point out to a potential chondroprotective role of COX-2 inhibitors, clinical studies did not investigate the intra-articular administration route and failed to confirm chondroprotective actions of systemically administered selective COX-2 inhibitors.

Discrepancies in chondroprotective actions of selective COX-2 inhibitors observed in the preclinical studies may be related to the route of administration. While six of the fourteen studies using systemic administration failed to demonstrate chondroprotective actions of selective COX-2 inhibitors, all studies that applied intra-articular bolus injections demonstrated chondroprotective actions. Interestingly, all clinical studies included in this systematic review evaluated

chondroprotective actions using the systemic administration route. Since these studies failed to demonstrate chondroprotective actions, it will be of interest to investigate the chondroprotective actions of selective COX-2 inhibitors using the intra-articular administration route for clinical studies. We did not encounter studies comparing chondroprotective effects of systemic versus intra-articularly administration of selective COX-2 inhibitors, but we believe this will be of interest to investigate in the future.

Improved chondroprotection of intra-articular injections with selective COX-2 inhibitor compared to a saline control condition may be related to increased bioavailability of the drug in the knee joint compared to systemic administrations. In addition, in a total joint disease such as knee OA [38][39][40][41], intra-articular administration of drugs may be more effective compared to systemic treatment due to the presence of scarcely vascularized tissues such as cartilage and meniscus [8]. Since COX-2 inhibitors can have an effect on all joint tissues, it is unclear whether the chondroprotective effect is a direct result of COX-2 inhibition in chondrocytes or an effect of COX-2 inhibition of other joint tissues.

Others and we failed to show a reduction of OA-related cartilage damage by celecoxib, when incorporated in an intra-articular drug delivery system [28][29]. It is a possibility that prolonged release of celecoxib may counteract potential chondroprotective effects due to increased loading of the affected joint indirectly caused by the analgesic effects of COX-2 inhibitors. These findings corroborate earlier observations in clinical studies, in which patients treated with anti-NGF demonstrated an increase in OA-related cartilage damage possibly due to joint overloading [5].

COX-2 inhibitors are expected to have anti-inflammatory effects by inhibiting the synthesis of prostanoids. Prostanoid subtypes are considered as inflammatory mediators [2] and are involved in cartilage degradation [3], but also in other pathophysiologic OA processes in different joint tissues such as synovial fibrosis and chondrocyte hypertrophy [42][43]. However, also anti-inflammatory actions of certain prostanoid subtypes have been shown [2], and therefore identifying downstream targets of the COX-2 pathway may further aid in anti-inflammatory treatment for knee OA. Inflammatory processes have been suggested to precede knee OA [4][44] and to be involved in structural disease progression [4]. A window of opportunity may exist, in which modulating the inflammatory status of the knee joint via intra-articular treatment with selective COX-2 inhibitors may lead to OA disease modification. The initiation of treatment may thus be important for the treatment outcome. The studies performed by Wen et al. [24] and Dai et al. [20] did not start treatment shortly after surgery and demonstrated chondroprotective actions of orally administered COX-2 inhibitors. It can be hypothesized that inhibiting inflammation directly after inducing a joint trauma may compromise cartilage regeneration, since inflammation is part of the early phases of natural tissue regeneration after a trauma [45]. This may explain why studies in surgical OA models fail to show chondroprotective effects when starting treatment directly after surgery. Moreover, the lack of a chondroprotective effect in clinical studies may be related to the stage of disease. Patients with knee OA are diagnosed in a stadium when the disease has progressed towards its end-stage [46], and it can be hypothesized that at this stage the disease is in an irreversible stadium where drug-based disease modification is not effective anymore. In addition, knee OA is a heterogeneous disease showing variability in the rate of disease progression in human subjects [47], while also the existence of distinct OA subtypes has been suggested [18][48], suggesting that patient-tailored drug treatment needs to be developed. Finally, the outcome measurements of clinical studies, such as joint space narrowing on conventional radiography, may not be sensitive enough. With the ongoing advancements in cartilage imaging [49], advanced techniques such as 7-tesla MRI imaging [49] may provide a more sensitive means to evaluate multiple outcome domains relevant to the clinical and pathophysiological aspects of disease modifying osteoarthritis drug (DMOAD)-mediated disease modification.

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