Q13. Can/should we develop guidelines to standardize the classification of studies testing for prophylactic versus therapeutic treatment effects?

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Response: YES
It is important to distinguish between prophylactic and therapeutic effects when considering pain outcomes, as this helps determine whether the intervention is changing pain secondarily by affecting structural disease or by targeting sensory nerves directly, i.e., a true analgesic. A small number of pain studies have addressed both prophylactic and therapeutic effects in the same publication. Standardized guidelines to help distinguish these could be generated using principles extrapolated from the published literature.

LEVEL OF EVIDENCE: Moderate

Delegate Vote: Agree: Disagree: Abstain:

Rationale:
Pain and structure correlate with one another.
The response above is dependent upon the concept that structural disease is related to the development of pain. Although the topic is sometimes regarded as controversial, there is good evidence that increases in pain are associated with worsening structural disease in both human and pre-clinical OA studies. That said, the correlation of patient-reported or pre-clinical measured pain behavior with structural disease is not very strong, especially when considering diverse human populations[1, 2]. Many extra-articular influences contribute to the pain experience beyond the primary nociceptive drive[3, 4]. In established human disease, synovial volume, bone marrow odema, cartilage loss and osteophyte volume all associate weakly with pain, and with one another[5, 6]. Multiple tissues may contribute to pain and these may change over the disease course [7]. The course of structural damage in preclinical models of OA depends on whether there is an acute inflammatory precipitant (e.g. monosodium iodoacetate or collagenase injection) or induction is by mechanical injury/joint destabilization in which case, damage is insidious and more akin to the clinical situation. Both show evidence of expected pathological changes in the joint, including cartilage damage, synovial thickening/inflammation, bone remodeling (osteophyte, subchondral sclerosis)[7-9]. Cartilage damage tends to be the metric that is universally reported in studies and has best score validity[10]. This does not necessarily mean that it is the cause of pain, but it can be regarded as a marker of pain-relevant structural disease. Indeed, Driscoll et al showed, using two different models of surgically induced OA in male mice, that onset of spontaneous pain behavior (by incapacitance testing) occurred at equivalent levels of cartilage damage even though they were occurring at different rates after surgical induction of disease[11]. Caution should be applied when considering the influence of biological sex, as onset of pain behavior occurs at earlier stages of structural disease severity in female rodents undergoing joint destabilization and with evidence of increased pain sensitivity[12, 13]. This aligns with higher pain scores for a given X-ray grade in female subjects (humans) with OA, possibly with contributions from changes in sex hormones[14-17].

Interventions that improve structural outcomes usually impact pain.
Testing of structural disease modifiers in preclinical studies is usually done prophylactically rather than therapeutically to optimize the chance of seeing a significant difference between control and intervention group. This may not be the most clinically relevant scenario. There are fewer studies that have looked at intervening later, at a stage when disease is already established. Choice of study design is often also restricted by the fact that the modification is genetic which may not allow for temporal control of gene deletion. Pain reduction in prophylactic studies where improvements in structural disease have been demonstrated is most likely due to the reduction in joint damage until proven otherwise. Relevant pain improvement may include a delay in pain onset, decrease in severity of pain or absence of pain over a defined study period. Examples of this include data from the *Adamts5*$^{-/-}$ mouse where there was significantly reduced cartilage damage after joint destabilization and reduction in mechanical allodynia[18, 19]. Neutralizing antibodies to Adamts5 given 4 weeks post-surgery (with evidence of early cartilage damage) changed the level of mechanical allodynia over the subsequent weeks in line with a change in joint damage[20]. No change in mechanical allodynia was observed with a single acute delivery of neutralizing antibody at 4 weeks post-surgical joint destabilization, providing further evidence that the effects on pain behavior were secondary to a change in structural disease[20]. To date, targeting ADAMTS5 in human studies has not shown success[21].

If better disease modifying treatments were available in humans, these could be used to validate therapeutic testing in preclinical models.

A true analgesic will target pain irrespective of structural damage and over a short time period (therapeutic delivery).

Analgesic agents should reduce established pain behavior in short term experiments after a short period of dosing. These agents may also show pain improvements after prophylactic dosing but with no evidence of structural disease modification. Pharmacological agents that have an established analgesic role in human disease management e.g. non-steroidal anti-inflammatory drugs (NSAIDS), have been shown to modulate established pain behavior in short-term challenges in preclinical OA models[22-24]. A good example of a more exploratory analgesic target in OA is nerve growth factor (NGF) where there is preclinical (murine, rat), dog, cat, and human validation of efficacy after its neutralization[25-29]. Further target validation is demonstrated by showing that NGF mRNA is up-regulated in joint tissues in OA[11, 30] and is temporally associated with the onset of pain behavior[11, 29]. The study by von Loga et al., showed reduction of spontaneous late OA pain behavior (beyond 8 weeks following partial meniscectomy in mice) with both prophylactic and therapeutic delivery of anti-NGF by vaccination, a response that correlated with the titre of anti-NGF measured in a sentinel cohort of mice[31]. Most of the aforementioned studies confirmed that there was no change in structural disease that could account for the effects on pain. Another example in surgically induced murine OA is shown following acute chemogenetic nociceptor silencing in mice in which an inhibitory designer receptor was co-expressed on sensory neurons that were Piezo2 positive. Targeting the designer receptor, by intraarticular injections of a synthetic ligand, showed an acute analgesic effect peaking 1h after activation[32]. A delay in onset of pain without a change in significant structural disease was also described in mice in which CCL2 or its receptor CCR2 were constitutively deleted[33, 34]. A direct analgesic mechanism for this observation was challenged when other groups showed structural modification after the CCL2-CCR2 axis was targeted[35, 36].

Limitations of current studies in preclinical models.

Defining times for “prophylactic” versus “therapeutic” intervention depend upon the preclinical model and likely mechanism of action of intervention. It is reasonable to define prophylactic as intervention before “structural disease” has occurred, and this is most usually defined as before evidence of cartilage damage, viewed by histology. Typically, treatment is started just prior to or around the time of disease induction (up to 7 days post induction) and pain is examined at a later time point, beyond the induction phase.

For therapeutic intervention there needs to be evidence of OA pathology (histologically or by radiography in larger animals) and evidence of established pain behavior. The complexity increases in view of the fact that different laboratories have described different patterns of pain behavior after induction of disease, including a prolonged phase of behavioral change that extends from the point of surgical or chemical induction and that is partly evident in the sham/vehicle group. Later pain behavior (defined by our group as at least 8-12 weeks after surgical destabilization in mice) may represent a safer period in which to assess “OA-related pain”. This period needs to be considered separately for each model, based on detailed time course studies. These considerations are also relevant to post traumatic OA in humans where the immediate injury related pain is unrelated to OA and OA-related pain develops insidiously over years after injury in a proportion of injured individuals[37]. Different modalities of pain behavior may show subtle differences too, although in our hands, mostly, these agree with one another[11] and many laboratories stick to trusted outcome measures that are deemed to be the most reliable in their hands.

Finally, there is a well-described difference in disease penetrance between male and female OA models, which is best described for mice. Female animals have reduced cartilage degradation scores compared with males, although they develop late “OA-related” pain at the same time as male mice[12]. In another study female mice were also shown to have prolonged period of hypersensitivity following surgical destabilization[38].The explanation for thes observations is unclear but a number of mechanisms have been proposed[12, 39, 40]. It would be prudent to examine male and female animals separately for these types of studies.

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