Development of medical therapeutics in osteoarthritis: time for action to improve patient care

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Osteoarthritis (OA) is one of the most common musculoskeletal conditions, affecting millions of people worldwide and placing a huge burden on healthcare systems (1). Not only is OA a major reason for joint surgery, including knee and hip replacements, but it is a serious disease since people with OA suffer with chronic pain, impaired function and increased risk of comorbidities, often over several decades of their lives (2). People with an OA diagnosis often require input from primary care and allied healthcare professionals, including physiotherapists, pharmacists and pain teams. Although the National Institute for Health and Care Excellence (NICE) in the UK recommends a holistic approach to the management of OA (3), there are many examples of underdiagnosis and lack of consistency of care being offered to people with OA (4), who may feel let down by healthcare professionals.

In comparison to other inflammatory conditions such as rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, it could be argued that progress with the development of disease-modulating or pain modifying therapies in OA has been slow. Part of the delay has been a lack of a full understanding of disease pathophysiology. While it is proven that cartilage damage and its loss is a major factor in OA pathogenesis, it is only recently that many researchers and clinicians have recognised OA as a disease of the whole joint (5). Acknowledgment that synovial tissue, ligaments, tendons and bone all play a role in disease pathophysiology and symptomatology in OA are important considerations in clinical trials of novel therapies which may translate into patient care (6).

Structural damage and how to modulate it to improve patient symptoms have been the ‘holy grail’ in OA research for some time. There is currently a strong pipeline of promising new pharmacological therapies for the modulation of structural damage/cartilage repair, with compounds in Phase 2/3 clinical trials, including wnt pathway inhibitors such as lorecivivint, ADAMTS-5 inhibitors, bisphosphonates such as zoledronic acid, cathepsin K inhibitors and sprifermin, a recombinant human fibroblast growth factor 18 (FGF-18), and agonist of FGFR2/3. However, recent trials showed that although agents such as sprifermin

improved cartilage thickness, such cartilage repair does not necessarily translate into immediate symptomatic improvement (7).

The mixed results from structure modification trials in OA have led some researchers to consider pain as a more clinically important treatment target in OA. After all, pain is often the main symptom, leading to significant impact on quality of life (8), and is what drives most people with OA to seek medical help (9). In the absence of more effective therapies, there may be a reliance on conventional analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and opiates, but these options are suboptimal because of their associated cardiovascular and gastrointestinal risks, and dependency/sedative side effects respectively (10). In recent years, significant advances have been made in understanding the neurobiology of pain in OA, including the recognition of pain sensitisation as an important feature (11). Molecular mediators of pain in OA include Nerve Growth Factor (NGF) as a peripheral mediator (12). It is interesting to note that whilst monoclonal neutralising antibodies to NGF such as tanezumab and fasinumab have been effective in the pain of large joint OA in Phase 2/3 trials (13, 14), this has not been the case for published clinical trials to date of inhibitors of the NGF receptor, TrkA (15). Other compounds may have efficacy in OA pain, including intra-articular capsaicin, which has previously only been available in topical form (16).

So where does this leave us in the management of OA? The prevalence of OA is set to rise in elderly populations and with the obesity epidemic. There remains a need to provide more effective, high quality multidisciplinary care for people with OA. During a patient journey, care should be optimised at every stage, including (and not bypassing) evidence-based core interventions with proven efficacy as disease modifiers including education, weight loss and exercise (3). Where first line interventions fail, well-defined pathways for input from different healthcare professionals including physiotherapy, rheumatology and orthopaedics should exist. A more holistic approach here is arguably needed, personalising the treatment

of this condition and supporting its self-management. Stratification tools can be developed to aid in the assessment and management of OA (17). By identifying pertinent disease features, it is conceivable that targeted and/or 'combination' therapy, something which has been effectively applied successfully in other conditions such as rheumatoid arthritis, could be considered for OA. For example, structure modification combined with pain modulation to achieve long-term disease modification in OA. Such interventions may require one or more drug interventions, combined with physical therapies (Figure 1). This combination therapy model relies on the efficacy of all the components for the outcome; critically, that pharmacological symptom improvement should allow people to gain maximal benefit by enabling physical therapies and improve outcome. Novel trial design remains challenging in OA and is crucial in testing such complex interventions, but also in assessing meaningful outcomes and effect size of interventions in OA, where changes may only occur over several years.

The promise of anti-NGF monoclonal antibodies as a new therapeutic option may prove desirable for some people with OA, particularly those who have failed to respond to first line treatments and who have an inadequate response to other pharmacological analgesia. With at least equivalent analgesic efficacy, anti-NGF monoclonal antibodies offer an alternative therapeutic option, without the unwelcome side effects and risks associated with NSAIDs and opiates (18). However, it should be noted that early trials of this therapeutic class were halted due to cases of rapidly progressive OA (RPOA); although this was in part found to correlate with higher doses and the co-prescription of NSAIDs, even with mitigation, this remains a consideration for this drug class (19). Careful medical screening and selection of patients, including the use of radiological assessment is likely to help reduce any potential adverse effects of this pain-relieving treatment, but follow up will be essential. Careful post marketing surveillance of potential adverse events including for RPOA and the drug's impact on other care pathways (negative or positive) will be needed, including adequate service provision to allow the safe prescribing and monitoring of these novel treatments. Real world data in the form of registries, such as has occurred in BSRBR will be necessary for

any biologics in OA to assess the longer-term benefits and risks of these therapies. Who will deliver this? Rheumatology, with its experience in biologic therapies in joint disease looks likely to be the critical overseer of any newly licensed drug classes, once NICE approved, and should ready itself for this step change.

There is an air of cautious optimism with such new therapies; opportunity is always balanced with potential risk. These are nevertheless exciting times for the treatment of OA, when new effective therapies like anti-NGF monoclonal antibodies may provide new hope for many with the disease. For health professionals who treat OA, we should look to optimise patient care working across disciplines.

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Conflicts of interest

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Figure 1 OA drug interventions, combined with physical therapies

Effective therapies for osteoarthritis are likely to involve a combination of therapies modifying joint structures and modulating pain symptoms. Pain can affect motivation to engage with other interventions like physical therapies which include exercise, joint bracing and splinting; effective pharmacological therapies should promote a more holistic approach to managing osteoarthritis.