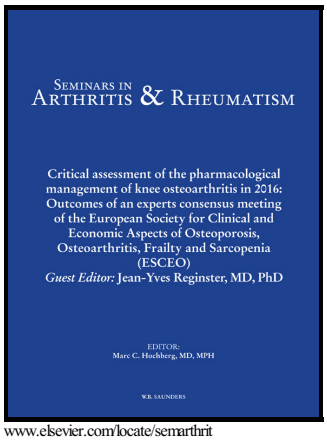
Biologic drugs as analgesics for the management of osteoarthritis

Dimitroulas, Theodoros ; Lambe, Tosin; Klocke, Rainer; Kitas, George D; Duarte, Rui

DOI:
10.1016/j.semarthrit.2016.12.001

Document Version
Peer reviewed version

Citation for published version (Harvard):
Dimitroulas, T, Lambe, T, Klocke, R, Kitas, GD & Duarte, R 2016, 'Biologic drugs as analgesics for the management of osteoarthritis', *Seminars in arthritis and rheumatism*.
https://doi.org/10.1016/j.semarthrit.2016.12.001



www.elsevier.com/locate/semarthrit

Biologic drugs as analgesics for the management of osteoarthritis

Theodoros Dimitroulas, Tosin Lambe, Rainer Klocke, George D. Kitas, Rui V. Duarte

PII: S0049-0172(16)30173-1
DOI: http://dx.doi.org/10.1016/j.semarthrit.2016.12.001
Reference: YSARH51133

To appear in: *Seminars in Arthritis and Rheumatism*

Cite this article as: Theodoros Dimitroulas, Tosin Lambe, Rainer Klocke, George D. Kitas and Rui V. Duarte, Biologic drugs as analgesics for the management of osteoarthritis, *Seminars in Arthritis and Rheumatism,* http://dx.doi.org/10.1016/j.semarthrit.2016.12.001

Biologic drugs as analgesics for the management of osteoarthritis

Theodoros Dimitroulas[a,b], Tosin Lambe[c], Rainer Klocke[a], George D Kitas[a,d], Rui V Duarte[c]

[a] Department of Rheumatology, Dudley Group NHS Foundation Trust, Dudley, UK

[b] Fourth Department of Internal Medicine, Hippokration University Hospital, Thessaloniki, Greece

[c] Institute of Applied Health Research, University of Birmingham, Birmingham, UK

[d] Arthritis Research UK Epidemiology Unit, Manchester University, Manchester, UK

Corresponding author: Rui Duarte, University of Birmingham, Institute for Applied Health Research, Murray Learning Centre, Room 124, B15 2TT, Birmingham, United Kingdom

Tel.: +44 (0) 121 414 7784; Email: r.duarte@bham.ac.uk

Conflict of interest statement: The authors have no conflicts of interest to declare.

Funding statement: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abstract

Background: Biologic drugs are novel therapeutic agents with demonstrated effectiveness in the management of a variety of chronic inflammatory disorders. Unmet needs in the treatment of chronic pain have led physicians to utilise a similar approach to patients suffering from conditions not characterised by systemic inflammation such as osteoarthritis (OA). The aim of this review is to discuss the current knowledge on the use of commonly used biologic agents (i.e. anti-tumour necrosis factor alpha (anti-TNF alpha) and anti-nerve growth factor (anti-NGF)) for the management of OA.

Methods: A narrative literature review of studies investigating the use of biologic agents for the management of osteoarthritis was conducted. We searched MEDLINE and EMBASE for English language publications. A hand-search of reference lists of relevant studies was also performed.

Results: Current evidence does not support TNF-alpha inhibition for the management of OA, although a selected subgroup of these patients with a marked inflammatory profile may benefit from this therapy. Anti-NGF therapy has been shown to reduce pain and improve function compared to placebo and non-steroidal anti-inflammatory drugs in OA but concerns remain regarding the safety of such treatment. The discrepant results observed in RCTs of biologic agents may be related to heterogeneity, small sample sizes and differences in the mode of administration of these drugs.

Conclusion: Anti-NGF therapy is efficacious for pain in patients with hip and knee OA. Despite the fact that current data suggests that anti-cytokine treatments have limited efficacy in patients with chronic osteoarthitic pain, larger and better designed studies in

more selected populations are justified to determine whether such therapeutic approaches can improve outcomes in this disabling condition where our medical treatment armamentarium is relatively poor.

Keywords: anti-nerve growth factor, anti-tumour necrosis factor alpha, biologic drugs, osteoarthritis

1. Introduction

Over the last decades advanced progress in biotechnology and pharmaceutical industry has been translated into the development of so-called biologic drugs, in particular monoclonal antibodies and fusion proteins. Based on their unique properties such as the exquisite selectivity with high affinity to the target, biologic molecules constitute a novel class of therapeutic agents which have transformed the management of a variety of refractory chronic rheumatic, gastrointestinal and cutaneous inflammatory disorders. As the routine administration of these regimens is expanding, the potential of fulfilling the growing and unmet needs in the treatment of chronic pain have prompted physicians to implement similar approaches in patients suffering from conditions not characterised by systemic inflammation such as osteoarthritis (OA) [1].

OA is probably the most common rheumatic condition affecting humans, characterized by chronic joint pain and considerable functional impairment as available pharmacological and non-pharmacological treatments have so far been of very limited value [2]. Although OA has historically been considered as a non-systemic inflammatory condition, a growing body of evidence supports the involvement of pro-inflammatory cytokines cascades in the development of cartilage degradation and loss, bone resorption and various levels of local, mainly synovial inflammation. Particularly, interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha) which are abundantly produced in osteoarthritic joints affect synoviocytes and chondrocytes to synthesize and excrete mediators and effectors of bone and synovial tissue turnover [3,4]. This inflammatory environment limits the capacity of chondrocytes to self-repair, and the ensuing imbalance between loss of cartilage and remodeling results in irreversible cartilage damage and

matrix degradation (Figure 1). Besides pro-inflammatory properties, TNF-alpha also activates central augmentation of pain and interacts with other neuro-inflammatory signaling systems and growth factors which are considered as key mediators in neuropathic component of osteoarthritic pain [5].

[Insert Figure 1 here]

Nerve growth factor (NGF) was the first discovered neurotrophic factor and it was primarily identified for its role in differentiation and survival of neurones in perinatal and early postnatal periods [6]. Recently, much focus has been given to its role in the perpetuation of chronic pain [7-9]. NGF is a secreted 13-kDa soluble neurotrophin polypeptide [10]. It binds to a non-selective 75 kDa neurotrophin receptor and a high-affinity NGF-selective tyrosine kinase receptor that are expressed on pain-transducing cells called nociceptors. Nociceptors send impulses to the central nervous system, where the conscious perception of pain is coordinated and appropriate physiological response is initiated. In the context of OA the upregulation of TNF and IL-1 in degenerated joints directly induce the expression of NGF in the inflamed tissue leading to increased overall activity of peripheral nociceptors and pain perception [11]. NGF also mediates pain indirectly by recruiting pro-inflammatory immune cells such as mast cells [12] that produce bradykinin, prostaglandin and NGF itself [13]. Intra-articularly, NGF upregulates local production of substance P and calcitonin gene-related peptide (CGRP), both of which are known to induce joint inflammation and degeneration. Although effective blockade of NGF does not directly promote joint tissue regeneration in

osteoarthritic joints, a reduction in inflammatory processes could allow for self-repair. Additionally, anti-NGF reduces both sensitivity to pain and frequency of spontaneous pain and this analgesic effect may also improve functionality and overall quality of life in patients.

Experimental and clinical studies confirming the role of anti-NGF in the pain pathway [8-10] as well as the appreciation that the inflammatory cytokine network contributes to the pathogenesis of OA [14] have underpinned the rationale for studies investigating whether such novel treatment approaches represent a potential treatment option for OA pain. Most of the trials have focused on TNF-alpha inhibitors but there are also reports with other anti-cytokine agents investigating the ability of biologic-based therapies to ameliorate pain in these highly prevalent and debilitating diseases. This review discusses the current knowledge on the use of biologic agents, specifically anti-TNF and anti-NGF for the management of osteoarthritis.

2. Methods

A MEDLINE and EMBASE search up to October 2016 was conducted according to published guidance on narrative reviews [15]. A combination of both indexing and free text terms was used including osteoarthritis, anti-TNF, anti-NGF, and growth factors. Studies were selected for inclusion if evaluating the use of biologic agents for the management of osteoarthritis. The search was restricted to articles published in English language but also included abstracts submitted in international congresses. A hand search of the reference lists of studies meeting the inclusion criteria was also performed to identify additional relevant reports.

3. Results

3.1. Tumour necrosis factor alpha inhibition

Given the dramatic effect of TNF-alpha inhibition on pain and structural damage in patients with inflammatory arthropathies, rheumatologists have tried to adopt similar therapeutic approaches for patients with osteoarthritis, predominantly individuals with erosive hand disease. However two double-blind, placebo-controlled trials did not demonstrate any superiority of adalimumab compared to placebo in patients with hand OA not responding to analgesic or anti-inflammatories in a follow-up period of 6-12 months [16,17]. In these studies TNF-alpha inhibition did not have any effect on structure modification, pain experience, number of painful or swollen joints nor reduced the consumption of analgesics in patients with OA; notably adalimumab halted the progression of bone erosions in the subgroup of patients with clinically swollen distal interphalangeal joints at baseline [16]. More recently a double-blind, placebo-controlled trial evaluating the efficacy of subcutaneous etanercept in patients with erosive OA of the hands provided promising results regarding the ability of the drug to improve pain and modify structural damage, again in patients with more symptomatic, inflammatory disease [18]. In the same study, etanercept was effective in improving bone marrow lesions predominantly in interphalangeal joints with inflammation at baseline, in a small number (n=20) of patients who underwent magnetic resonance imaging [19]. However in the whole study population, no difference between etanercept and placebo was observed in visual analogue score pain at 24 weeks. Open-label studies have reported similar results [20] with the exception of a single-blind study on 10 patients in which intraarticular injection of infliximab reduced joint pain and tenderness on palpation when

individual joints were assessed [21]. Intraarticular administration of the IL-1 receptor antagonist, anakinra, failed to provide clinical benefit in patients with knee OA in a double-blind placebo RCT [22]. Table 1 summarizes the studies employed anti-cytokine biologic drugs in OA individuals.

Table 1 Studies with TNF-alpha inhibitors in OA patients

Study	Design	Patients/ Controls	Molecule	Intervention	Primary end point (months)	Outcomes
Chevalier et al 2015 [17]	RCT	41/42	ADA	40mg SC/ 2weeks	6/12	(-) VAS
Chevalier et al 2009 [22]	RCT	101/69	ANA	50mg IA/ 150mg	3/12	(-) WOMAC
Fioravanti et al 2009 [21]	Open-label	10	INF	0.2 ml IA	12/12	Improvement of symptoms
Kloppenburg et al [18]	RCT	45/45	ETA	50mg SC/ week (24 weeks) 25mg SC/week (24 weeks)	12/12	↓VAS in subgroup with swollen joints
Magnano et al 2007 [20]	Open-Label	12	ADA	40mg SC/ 2 weeks	3/12	(-) OMERACT
Verbruggen et al 2012 [16]	RCT	30/30	ADA	40mg SC/ 2weeks	12/12	↓GUSS in subgroup with swollen joints

ADA: adalilumab, ANA: anakinra, ETA: etanercept, GUSS: Ghent University Scoring System, IA: intraarticularly, INF: infliximab, OMERCAT: outcome measures in rheumatology, RCT: randomized-controlled study, SC: subcutaneous, VAS: visual analogue score, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

3.2. Nerve growth factor inhibition

The potential use of anti-NGF has been explored in several chronic pain conditions but osteoarthritis of the hip and knee being the primary indication for the majority of clinical trials (Table 2).

Unlike the unflattering results from TNF-alpha inhibition, results from clinical trials clearly demonstrate that anti-NGF reduces pain and improves functions compared to

placebo and non-steroidal anti-inflammatory drugs in patients with osteoarthritis of either the hip or knee. Naproxen, diclofenac, oxycodone and celecoxib are analgesics with good efficacy in osteoarthritis that have often been used as active comparators in anti-NGF trials [23,24]. A systematic review of twelve clinical trials showed the unequivocal efficacy of anti-NGF compared to placebo and other active comparator in hip and knee OA [25]. A noteworthy point in the review was that the standardised effect size in phase II trials where study drug was administered on µg/kg basis were greater that Phase III trials where fixed doses were administered. However, pharmacokinetic analysis of three of the phase III trials included in the review concluded that minimal variability exists between fixed versus weight-adjusted dosing, thus indicating that other patient-level factors may be responsible for the observed efficacy difference between phase II and III trials [26].

Study	Patients in treatment arm	Molecule	Intervention	Control treatment	Primary end point (months)	Outcomes
Balanescu et al 2014 [27]	453	TAN	3 IV infusion/ 8 weeks	Placebo + Diclofenac	4/12	↓ WOMAC ↓ PGA ↔ AE
Brown et al 2012 [28]	518	TAN	3 IV injection/ 8 weeks	Placebo	4/12	↓ WOMAC ↓ PGA ↑ AE
Brown et al 2013 [29]	466	TAN	3 IV injection/ 8 weeks	Placebo	4/12	↓ WOMAC ↓ PGA ↑ AE
Ekman et al 2011 [30]	624	TAN	2 IV injection/ 8 weeks	Naproxen/Placebo	4/12	↓ WOMAC ↓ PGA ↑ AE
Lane et al 2010 [31]	375	TAN	2 IV injection/ 8 weeks	Placebo	4/12	↓ WOMAC ↓ PGA ↑ AE
Maloney et al 2016 [32]	419	FNB	3 SC injection/ 12 weeks	Placebo	4/12	↓ WOMAC ↓ PGA
Mayorga et al 2011 [33]	98	FLN	3 SC injection/ 8 weeks	Oxycodone/Placebo	3/12	↓ WOMAC ↑TEAE
Nagashima et al 2011 [34]	67	TAN	Single IV injection	Placebo	4/12	↓ Knee pain index ↓WOMAC ↔TEAE
Sanga et al 2013 [35]	356	FLN	3 SC injection/4 weeks; 2 SC injection/8 weeks	Placebo	4/12	↓ OAPI ↓ WOMAC ↔TEAE
Schnitzer et al 2015 [36]	2,161	TAN	2 IV injection/ 8 weeks	Naproxen/Celecoxib	4/12	↓WOMAC ↑OMERACT-OARSI ↑AE
Spierings et al 2013 [37]	472	TAN	2 IV infusion/ 8 weeks	Oxycodone/Placebo	4/12	↓ WOMAC ↓ PGA ↑ AE
Tiseo et al 2014 [38]	160	FNB	2 IV infusion/ 8 weeks	Placebo	24/12	↔ TEAE ↓ WOMAC ↑PGIC

Table 2 Phase II and III clinical trials of anti-NGF agents for osteoarthritis

AE: adverse event; FLN: fulranumab, FNB: fasinumab, IV: intravenous, OAPI: osteoarthritis pain intensity, OMERACT-OARSI: Outcome Measures in Rheumatology-Osteoarthritis Research Society

International, PGA: patient's global assessment, PGIC: Patient Global Impression of Change, SC: subcutaneous, TAN: tanezumab, TEAE: treatment-emergent adverse event, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

4. Discussion

Over the last decades advances in the understanding of OA pathophysiology have illustrated that inflammatory cytokine network is substantially involved in initiation and propagation of structural bone and cartilage tissues changes. Therefore the use of biologic molecules targeting specific inflammatory and pain signaling pathways to ameliorate chronic osteoarthritic pain is based on a sound rationale.

Clinical research results however did not meet the expectations as three double blind placebo controlled studies conducted in patients with erosive inflammatory arthritis of the hands failed to demonstrate superiority of TNF-alpha inhibitors in terms of pain scores and functional improvement [16,18,20]. On the other hand the findings of these trials indicate that specific subsets of OA individuals with erosive hand disease may benefit from biologic drugs. Particularly the subset of patients with a pronounced inflammatory element contributing to the symptoms appear to respond better and more importantly may represent the best target population for future trials. In that respect recent reports from ultrasound based studies suggesting that ultrasound determined synovitis in the small joints of the hands is an independent predictor of the development of joint erosions at 2 [39] and 4 years [40] lend more support to the concept that enhanced residual inflammatory activity may represent a potential target for research in this particular subgroup of patients.

Of course the launch of future studies investigating the effect of TNF-alpha inhibition on OA should be considered against the background of limitations particularly in view of high costs. The limited effect of biologic drugs demonstrated to-date raises doubts for the cost-effectiveness of trials in this field, however the high economic burden and the social consequences associated with OA [41] as well as the failure of other treatment approaches – for example a recently presented negative double blind placebo-controlled hydroxychloroquine trial [42] - emphasize the need for better therapeutic strategies in OA, still a neglected disease [43]. Current financial constraints mandate the implementation of value-based medicine and in this regard the identification of patients more likely to benefit from biologic drugs using ultrasound as a screening tool for future trials and the potential introduction of biosimilars [44] may reduce the costs of biotherapy given that RCTs with hard end-points may confirm the effectiveness of these regimens in OA of the hands.

Whereas NGF blockade has been quite effective in patients with OA of the knee and the hip, safety considerations forced US Food and Drug Administration (FDA) to suspend trials on anti-NGF mAb in 2010 due to reported cases of osteonecrosis that led to total joint replacement, and severe peripheral neuropathy in trials. The adverse event profile in other anti-NGF trials for osteoarthritis, which suggested class effect, was particularly crucial in tipping the FDA's decision to suspend the trials except for patients with terminal cancer [45]. Although the FDA decision has been reversed in 2012, the concern over adverse events remains. No clear association between anti-NGF and osteonecrosis has been demonstrated as rapidly progressive joint degeneration can be considered as a natural course of OA in some patients and osteonecrosis can also co-exist with OA at

some stage [46]. Osteonecrosis has not been observed in trials assessing the effect in other chronic conditions, demonstrating the importance of patient characteristics [47]. Another proposed indirect reason for the relatively higher incidence of joint destruction in patients receiving anti-NGF is based on the assumption that pain reduction encourages increased joint activity and overloading [45,48]. A recent animal model seems to support this idea [49]. While these are plausible reasons, OA treatments should aim to reduce pain and, to a reasonable extent, improve function. Successful treatments may result in patients resuming normal activity which may inadvertently lead to additional pressure on the joint. As with any other drug, the benefit-risk ratio of treatment with anti-NGF for OA should therefore be carefully considered by clinicians and patients.

Although data is inconsistent, it appears that biologic molecules are not effective in improving pain and outcomes in patients with severe OA. Targeting of other cytokine signaling pathways such as IL-1 – there is currently a planned trial [50] - IL-6 and IL-17 should be investigated. The latter may play in role in the activation of chondrocytes and production of inflammatory mediators but no clinical data is available to-date [14]. Biologic drugs blocking the inflammatory properties of IL-17 are successfully used in the spondyloarthropathies [51] but their effectiveness in OA has not been explored. The delineation of complex mechanisms of osteoarthritic pain and the recognition of a neuropathic component with central pain perception have shed more light in our understanding of chronic pain in this condition [52]. Novel therapies blocking central pain sensitization pathways are under investigation and may open new avenues in optimization of pain management in OA.

5. Conclusion

Optimal management of chronic pain and disability in conditions such as osteoarthritis in which locally produced inflammatory cytokines and central pain perception interfere with each other remains an unmet need in the modern treatment era. The discovery and development of biologic molecules as well as the ultimate utilization of cytokine-targeted therapies for analgesia in these conditions is very much in the ascendance. RCTs have not met the initial expectations based on case reports regarding the ability of biologics to replenish the supply of novel therapies in pain control and transform the standard of care in the same way that such regimens have achieved for inflammatory arthropathies. Effective inhibition of NGF pathway has proved efficacy in alleviating pain and improving functional status particularly in patients with large joint involvement but concerns about the safety have delayed translation and validation of these findings in the daily routine clinical setting. The better understanding of the complex mechanisms, the cytokine networks and the mediators contributing to the clinical presentation and long term outcomes in these conditions have shifted the treatment paradigm towards the whole system responsible for the development of chronic pain including neuropathic type of pain, as therapies targeting one single cytokine or component of pain appear to have limited effect. Inter-individual variations in pain perception and persistence should also be taken into consideration in the design and the interpretation of results of future trials. Larger and better designed studies particularly in respect of, doses ranges, treatment administration intervals and sub-group definition of disease, may be more likely to identify a future clinical role of biologic drugs in these conditions taking always into account the cost-effectiveness of such therapeutic strategies.

References

[1] Chessell IP, Dudley A, Billinton A. Biologics: the next generation of analgesic drugs? Drug Discov Today 2012;17:875-9.

[2] Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012;64:465-74.

[3] Westacott CI, Sharif M. Cytokines in osteoarthritis: mediators or markers of joint destruction? Semin Arthritis Rheum 1996;25:254-72.

[4] Simão AP, Almeida TM, Mendonça VA, Santos SA, Gomes WF, Coimbra CC, Lacerda AC. Soluble TNF receptors are produced at sites of inflammation and are inversely associated with self-reported symptoms (WOMAC) in knee osteoarthritis. Rheumatol Int 2014;34:1759-63.

[5] Leung L, Cahill CM. TNF-alpha and neuropathic pain--a review. J Neuroinflammation 2010;7:27.

[6] Mantyh PW1, Koltzenburg M, Mendell LM, Tive L, Shelton DL. Antagonism of nerve growth factor-TrkA signaling and the relief of pain. Anesthesiology 2011;115:189-204.

[7] Oddiah D, Anand P, McMahon SB, Rattray M. Rapid increase of NGF, BDNF and NT-3 mRNAs in inflamed bladder. Neuroreport 1998;9:1455-8.

[8] Kumar V, Mahal BA. NGF - the TrkA to successful pain treatment. J Pain Res 2012;5:279-87.

[9] Pezet S, McMahon SB. Neurotrophins: mediators and modulators of pain. Annu Rev Neurosci 2006;29:507-38.

[10] Maliartchouk S, Saragovi HU. Optimal nerve growth factor trophic signals mediated by synergy of TrkA and p75 receptor-specific ligands. J Neurosci 1997;17:6031-7.

[11] Eibl JK, Strasser BC, Ross GM. Structural, biological, and pharmacological strategies for the inhibition of nerve growth factor. Neurochem Int 2012;61:1266-75.

[12] Kawamoto K, Aoki J, Tanaka A, Itakura A, Hosono H, Arai H, Kiso Y, Matsuda H. Nerve growth factor activates mast cells through the collaborative interaction with lysophosphatidylserine expressed on the membrane surface of activated platelets. J Immunol 2002;168:6412-9.

[13] Petersen M, Segond von Banchet G, Heppelmann B, Koltzenburg M. Nerve growth factor regulates the expression of bradykinin binding sites on adult sensory neurons via the neurotrophin receptor p75. Neuroscience 1998;83:161-8.

[14] Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol 2011;7:33-42.

[15] Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD. Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. Rheumatol Int 2011;31:1409–17.

[16] Verbruggen G, Wittoek R, Vander Cruyssen B, Elewaut D. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints:

a double blind, randomised trial on structure modification. Ann Rheum Dis 2012;71:891-8.

[17] Chevalier X, Ravaud P, Maheu E, Baron G, Rialland A, Vergnaud P, Roux C, Maugars Y, Mulleman D, Lukas C, Wendling D, Lafforgue P, Loeuille D, Foltz V, Richette P; On behalf of the French section of osteoarthritis. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. Ann Rheum Dis 2015;74:1697-705.

[18] Kloppenburg M, Ramonda R, Kwok WY, Bobacz K, Elewaut D, Frallonardo P, Huizinga TW, Kroon F, Smolen J, Vander Cruyssen B, Wolterbeek R, Punzi L, Verbruggen G, Wittoek R. Randomized, Placebo-Controlled Trial To Evaluate Clinical Efficacy and Structure Modifying Properties of Subcutaneous Etanercept (ETN) in Patients with Erosive Inflammatory Hand Osteoarthritis (OA). Ann Rheum Dis 2016;75:90-91.

[19] Kroon FP, Wittoek R, Verbruggen G, Haugen IK, Huizinga TW, Kloppenburg M. Effect of Etanercept on Synovitis and Bone Marrow Lesions in Erosive Hand Osteoarthritis. Ann Rheum Dis 2016;75:91-92.

[20] Magnano MD, Chakravarty EF, Broudy C, Chung L, Kelman A, Hillygus J, Genovese MC. A pilot study of tumor necrosis factor inhibition in erosive/inflammatory osteoarthritis of the hands. J Rheumatol 2007;34:1323-7.

[21] Fioravanti A, Fabbroni M, Cerase A, Galeazzi M. Treatment of erosive osteoarthritis of the hands by intra-articular infliximab injections: a pilot study. Rheumatol Int 2009;29:961-5.

[22] Chevalier X, Goupille P, Beaulieu AD, Burch FX, Bensen WG, Conrozier T, Loeuille D, Kivitz AJ, Silver D, Appleton BE. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2009;61:344-52.

[23] Lohmander LS, McKeith D, Svensson O, Malmenäs M, Bolin L, Kalla A, Genti G, Szechinski J, Ramos-Remus C; STAR Multinational Study Group. A randomised, placebo controlled, comparative trial of the gastrointestinal safety and efficacy of AZD3582 versus naproxen in osteoarthritis. Ann Rheum Dis 2005;64:449-56.

[24] Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000;284:1247-55.

[25] Schnitzer TJ, Marks JA. A systematic review of the efficacy and general safety of antibodies to NGF in the treatment of OA of the hip or knee. Osteoarthritis Cartilage 2015;23:S8-17.

[26] Jonsson EN, Xie R, Marshall SF, Arends RH. Population pharmacokinetics of tanezumab in phase 3 clinical trials for osteoarthritis pain. Br J Clin Pharmacol 2016;81:688-99.

[27] Balanescu AR, Feist E, Wolfram G, Davignon I, Smith MD, Brown MT, West CR. Efficacy and safety of tanezumab added on to diclofenac sustained release in patients

with knee or hip osteoarthritis: a double-blind, placebo-controlled, parallel-group, multicentre phase III randomised clinical trial. Ann Rheum Dis 2014;73:1665-72.

[28] Brown MT, Murphy FT, Radin DM, Davignon I, Smith MD, West CR. Tanezumab reduces osteoarthritic knee pain: results of a randomized, double-blind, placebo-controlled phase III trial. J Pain 2012;13:790-8.

[29] Brown MT, Murphy FT, Radin DM, Davignon I, Smith MD, West CR. Tanezumab reduces osteoarthritic hip pain: results of a randomized, double-blind, placebo-controlled phase III trial. Arthritis Rheum 2013;65:1795-803.

[30] Ekman E, Gimbel J, Bello A, Smith M, Keller D, Annis K, Brown M, West C, Verburg K. Efficacy and safety of intravenous tanezumab in osteoarthritis hip and knee pain: comparison to placebo and naproxen in two phase III studies (NCT00830063 & NCT00863304). J Pain 2011;12:P55.

[31] Lane NE, Schnitzer TJ, Birbara CA, Mokhtarani M, Shelton DL, Smith MD, Brown MT. Tanezumab for the treatment of pain from osteoarthritis of the knee. N Engl J Med 2010;363:1521-31.

[32] Maloney J, Kivitz A, Schnitzer TJ, Dakin P, Stehman-Breen C, Geba G. Efficacy and Safety of Fasinumab for Osteoarthritic Pain in Patients with Moderate to Severe Osteoarthritis of the Knees or Hips [abstract]. Arthritis Rheumatol 2016;68 (suppl 10).

[33] Mayorga A, Wang S, Wang S, Kelly K, Thipphawong J. Double-blind, randomized study to evaluate efficacy, and safety of fulranumab in patients with moderate to severe, chronic knee pain from osteoarthritis: interim analysis results. J Pain 2013;4:S69.

[34] Nagashima H1, Suzuki M, Araki S, Yamabe T, Muto C; Tanezumab Investigators. Preliminary assessment of the safety and efficacy of tanezumab in Japanese patients with moderate to severe osteoarthritis of the knee: a randomized, double-blind, dose-escalation, placebo-controlled study. Osteoarthritis Cartilage 2011;19:1405-12.

[35] Sanga P, Katz N, Polverejan E, Wang S, Kelly KM, Haeussler J, Thipphawong J. Efficacy, safety, and tolerability of fulranumab, an anti-nerve growth factor antibody, in the treatment of patients with moderate to severe osteoarthritis pain. Pain 2013;154:1910-9.

[36] Schnitzer TJ, Ekman EF, Spierings EL, Greenberg HS, Smith MD, Brown MT, West CR, Verburg KM. Efficacy and safety of tanezumab monotherapy or combined with non-steroidal anti-inflammatory drugs in the treatment of knee or hip osteoarthritis pain. Ann Rheum Dis 2015;74:1202-11.

[37] Spierings EL, Fidelholtz J, Wolfram G, Smith MD, Brown MT, West CR. A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. Pain 2013;154:1603-12.

[38] Tiseo PJ, Kivitz AJ, Ervin JE, Ren H, Mellis SJ. Fasinumab (REGN475), an antibody against nerve growth factor for the treatment of pain: results from a double-blind, placebo-controlled exploratory study in osteoarthritis of the knee. Pain 2014;155:1245-52.

[39] Kortekaas MC, Kwok WY, Reijnierse M, Stijnen T, Kloppenburg M. Brief Report: Association of Inflammation With Development of Erosions in Patients With Hand Osteoarthritis: A Prospective Ultrasonography Study. Arthritis Rheumatol 2016;68:392-7.

[40] Mancarella L, Addimanda O, Pelotti P, Pignotti E, Pulsatelli L, Meliconi R. Ultrasound detected inflammation is associated with the development of new bone erosions in hand osteoarthritis: a longitudinal study over 3.9 years. Osteoarthritis Cartilage 2015;23:1925-32.

[41] Xie F, Kovic B, Jin X, He X, Wang M, Silvestre C. Economic and Humanistic Burden of Osteoarthritis: A Systematic Review of Large Sample Studies. Pharmacoeconomics 2016;34:1087-1100.

[42] Kingsbury SR, Tharmanathan P, Keding A, Ronaldson S, Grainger A, Wakefield RJ, Arundel C, Birrell F, Doherty M, Vincent T, Watt FE, Dziedzic K, O'Neill TW, Arden NK, Scott DL, Dickson J, Garrood T, Green M, Menon A, Sheeran T, Torgerson D, Conaghan PG. Hydroxychloroquine Is Not Effective in Reducing Symptoms of Hand Osteoarthritis: Results from a Placebo-Controlled Randomised Trial [abstract]. Arthritis Rheumatol 2016;68(suppl 10).

[43] Hill S, Dziedzic KS, Nio Ong B. Patients' perceptions of the treatment and management of hand osteoarthritis: a focus group enquiry. Disabil Rehabil 2011;33:1866-72.

[44] Lakhanpal A, Brahn E. Biosimilars in rheumatic diseases: structural and functional variability that may impact clinical and regulatory decisions. Clin Rheumatol 2016: In press.

[45] Holmes D. Anti-NGF painkillers back on track? Nat Rev Drug Discov 2012;11:337-8.

[46] Hochberg MC, Abramson SB, Hungerford DS, McCarthy E, Vignon EP, Smith MD, Tive L. Adjudication of reported serious adverse joint events in the tanezumab clinical development program. Arthritis Rheum 2012;64:260.

[47] Kumar P, Clark M. Kumar & Clark Clinical Medicine. 6th ed. New York: W.B. Saunders; 2005.

[48] Smelter E1, Hochberg MC. New treatments for osteoarthritis. Curr Opin Rheumatol 2013;25:310-6.

[49] Ishikawa G, Koya Y, Tanaka H, Nagakura Y. Long-term analgesic effect of a single dose of anti-NGF antibody on pain during motion without notable suppression of joint edema and lesion in a rat model of osteoarthritis. Osteoarthritis Cartilage 2015;23:925-32.

[50] Evans CH. A Phase I Study Evaluating the Safety of Intra-Articular Sc-rAAV2.5IL-1Ra in Subjects With Moderate Osteoarthritis of the Knee (NCT02790723). In: ClinicalTrials.gov [Internet]

[51] Lubrano E, Perrotta FM. Secukinumab for ankylosing spondylitis and psoriatic arthritis. Ther Clin Risk Manag 2016;12:1587-92.

[52] Dimitroulas T, Duarte RV, Behura A, Kitas GD, Raphael JH. Neuropathic pain in osteoarthritis: A review of pathophysiological mechanisms and implications for treatment. Semin Arthritis Rheum 2014;44:145-54.

Figure 1 Mechanisms of pain and biologic treatment targets in osteoarthritic joint

Activated macrophage synoviocytes and chondrocytes produce pro-inflammatory mediators which in turn activate peripheral nociceptors that innervate the synovial capsule, periosteum and subchondral bone contributing to peripheral sensitization and hyperexcitability of nociceptive neurons in the central nervous system. Neurotrophic factors, predominantly NGF further exacerbate joint destruction process and inflammation by upregulating neuropeptides such as calcitonin gene-related peptide and substance P which promote mechanical sensitization of the joint. Blockade of these pathways may diminish the degree of immune responses with direct and indirect beneficial effects on joint degeneration and pain perception. Cytokine-targeted pathways reduce the synthesis and release of intra-articular mediators while inhibition of NGF-mediated pathways may result in the reduction of synovial inflammation and alleviation of pain symptoms.

IL-1: interleukin-1, NGF: nerve growth factor, TNF-alpha: tumor necrosis factor-alpha.