Biologic drugs as analgesics for the management of osteoarthritis

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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 utilize a similar approach to patients suffering from conditions not characterized 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-tumor 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 osteoarthritic 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.

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 characterized 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 synovio-
cytes and chondrocytes to synthesize and excrete mediators and
effectors of bone and synovial tissue turnover [3,4]. This inflamma-
tory 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 (Fig.).
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].

Nerve growth factor (NGF) was the first discovered neuro-
trophic factor and it was primarily identified for its role in
differentiation and survival of neurons 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 patho-
genesis 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.

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.

Results

Tumor 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 indi-
viduals 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-inflammatory modifiers in a follow-up
period of 6–12 months [16,17]. In these studies, TNF-alpha inhibi-
tion did not have any effect on structure modification, pain
experience, number of painful or swollen joints nor reduce the
consumption of analgesics in patients with OA; notably adalimu-
mab 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 analog 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
intra-articular injection of infliximab reduced joint pain and
tenderness on palpation when individual joints were assessed
[21]. Intra-articular 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.
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 12 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 standardized effect size in phase II trials where study drug was administered on mg/kg basis were greater than 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].

Table 1
Studies with TNF-alpha inhibitors in OA patients

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


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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients in treatment arm</th>
<th>Molecule</th>
<th>Intervention</th>
<th>Control treatment</th>
<th>Primary end point (months)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balanescu et al. [27]</td>
<td>453</td>
<td>TAN</td>
<td>3 IV infusion/8 weeks</td>
<td>Placebo + diclofenac</td>
<td>4/12</td>
<td>↓ WOMAC</td>
</tr>
<tr>
<td>Brown et al. [28]</td>
<td>518</td>
<td>TAN</td>
<td>3 IV injection/8 weeks</td>
<td>Placebo</td>
<td>4/12</td>
<td>↓ WOMAC, ↓ PGA</td>
</tr>
<tr>
<td>Brown et al. [29]</td>
<td>466</td>
<td>TAN</td>
<td>3 IV injection/8 weeks</td>
<td>Placebo</td>
<td>4/12</td>
<td>↓ WOMAC, ↓ PGA, ↑ AE</td>
</tr>
<tr>
<td>Ekman et al. [30]</td>
<td>624</td>
<td>TAN</td>
<td>2 IV injection/8 weeks</td>
<td>Naproxen/placebo</td>
<td>4/12</td>
<td>↓ WOMAC, ↓ PGA, ↑ AE</td>
</tr>
<tr>
<td>Lane et al. [31]</td>
<td>375</td>
<td>TAN</td>
<td>2 IV injection/8 weeks</td>
<td>Placebo</td>
<td>4/12</td>
<td>↓ WOMAC, ↓ PGA, ↑ AE</td>
</tr>
<tr>
<td>Maloney et al. [32]</td>
<td>419</td>
<td>FNB</td>
<td>3 SC injection/12 weeks</td>
<td>Placebo</td>
<td>4/12</td>
<td>↓ WOMAC, ↓ PGA</td>
</tr>
<tr>
<td>Mayorga et al. [33]</td>
<td>98</td>
<td>FLN</td>
<td>3 SC injection/8 weeks</td>
<td>Oxycodone/placebo</td>
<td>3/12</td>
<td>↓ WOMAC, ↑ TEAE</td>
</tr>
<tr>
<td>Nagashima et al. [34]</td>
<td>67</td>
<td>TAN</td>
<td>Single IV injection</td>
<td>Placebo</td>
<td>4/12</td>
<td>↓ Knee pain index</td>
</tr>
<tr>
<td>Sanga et al. [35]</td>
<td>356</td>
<td>FLN</td>
<td>3 SC injection/4 weeks; 2 SC injection/8 weeks</td>
<td>Placebo</td>
<td>4/12</td>
<td>↓ WOMAC, ↑ OAPI</td>
</tr>
<tr>
<td>Schnitzer et al. [36]</td>
<td>2161</td>
<td>TAN</td>
<td>2 IV injection/8 weeks</td>
<td>Naproxen/celecoxib</td>
<td>4/12</td>
<td>↓ WOMAC, ↑ TEAE, ↓ WOMAC, ↓ OMERACT-OARSI, ↑ AE</td>
</tr>
<tr>
<td>Spierings et al. [37]</td>
<td>472</td>
<td>TAN</td>
<td>2 IV infusion/8 weeks</td>
<td>Oxycodone/placebo</td>
<td>4/12</td>
<td>↓ WOMAC, ↓ PGA</td>
</tr>
<tr>
<td>Tiseo et al. [38]</td>
<td>160</td>
<td>FNB</td>
<td>2 IV infusion/8 weeks</td>
<td>Placebo</td>
<td>24/12</td>
<td>↓ WOMAC, ↑ TEAE, ↑ PGIC</td>
</tr>
</tbody>
</table>

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.

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 use 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. 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 subgroup 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

[4] Simão AP, Almeida TM, Mendonça VA, Santos SA, Gomes WF, Coimbra CG, et al. Soluble TNF receptors are produced at sites of inflammation and are


