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NERVE GROWTH FACTOR (NGF) BLOCKADE FOR THE MANAGEMENT OF OSTEOARTHRITIS PAIN: WHAT CAN WE LEARN FROM CLINICAL TRIALS AND PRECLINICAL MODELS?

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Abstract

Purpose of review—Anti-NGF antibodies hold tremendous potential for the management of osteoarthritis (OA) pain, but clinical trials have revealed serious adverse effects that are incompletely understood. This review discusses clinical trial results along with preclinical studies that have assessed NGF blockade in experimental OA, in order to provide insight for future studies.

Recent findings—Systematic reviews have revealed that anti-NGF therapy, including tanezumab, is efficacious in improving pain and function, but serious adverse events, including rapidly progressive OA and osteonecrosis, resulted in a moratorium on trials that was only recently lifted. Within the past year, preclinical testing has revealed effects of NGF blockade on both pain behaviors and joint structure in experimental models of OA. Similar to clinical trial results, these studies in laboratory animals demonstrated analgesic efficacy of NGF blockade. Interestingly, several animal studies have suggested detrimental effects on joint integrity as a result of treatment, particularly when treatment is started early in the disease, when joint damage is mild to moderate.

Summary—NGF blockade continues to represent a promising new approach for the treatment of OA pain, but the actual benefits and risks remain to be fully elucidated. Preclinical models may suggest patient populations that could be best served while limiting side effects, but future work should further investigate the mechanisms of benefits and unwanted side effects.

Keywords

Nerve growth factor; TrkA; osteoarthritis; pain; animal models

INTRODUCTION

Nerve growth factor (NGF) was discovered by Rita Levi-Montalcini in 1952, and her subsequent work with Stanley Cohen in the 1950s demonstrated that this soluble factor controlled the growth and development of the nervous system (1). In the 1990s, it was recognized that in adults, NGF plays a role in tissue injury and pain (2, 3). As a member of the neurotrophin family, NGF can bind the general neurotrophin receptor p75, as well as its

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high-affinity cognate receptor, tropomyosin-related kinase (Trk)A (4). The NGF-TrkA pathway in particular appears to be critical in driving acute and chronic pain (4). In addition to the nervous system, NGF can be expressed by and act on a variety of non-neuronal cells, including inflammatory cells, keratinocytes, endothelial cells (4), and cells within the joint such as chondrocytes (5). This narrative review will briefly discuss results from anti-NGF clinical trials for osteoarthritis (OA) pain. In addition, we will review the emerging literature on the effects of NGF blockade in experimental models of OA, in order to examine whether preclinical observations can provide insight into the clinical findings, in particular the reported adverse effects. We searched Pubmed for the following keywords: “Nerve growth factor”, “TrkA”, “osteoarthritis”, “pain”, “clinical trials”, “animal models”. The basic mechanisms of action of NGF, the effects of NGF blockade in preclinical models of other types of pain, and details on expression of NGF and TrkA in the joint are beyond the scope of this review, but other recent reviews covering these topics are available (for examples, see (3–6)).

NERVE GROWTH FACTOR TARGETED THERAPY: CLINICAL IMPLICATIONS

Inadequate pain relief is the most troubling aspect of OA to patients and is responsible for the majority of OA-related physician visits. Concerns about potential risks with prolonged use of NSAIDs and opiates have left the therapeutic armamentarium for OA grossly depleted. As such, pain control remains the most significant unmet need in OA management.

NGF has long been an attractive therapeutic target for OA pain, and expectations increased following publication of the first well-powered controlled trial of anti-NGF therapy in OA in 2010 (7). Shortly afterwards, however, the US FDA imposed a hold on all clinical trials of NGF antagonists because of reports of rapidly progressive OA and of osteonecrosis (ON) among patients receiving these agents; subsequently, this hold was extended due to observations of autonomic nervous damage in preclinical models (8). The hold was ultimately lifted in 2015, and development targeted at refractory knee or hip OA pain is again proceeding rapidly.

There are at least four monoclonal antibody-based NGF antagonists in various stages of development; tanezumab is the most advanced and is in Phase III clinical trials, whereas fulranumab, fasinumab, and ABT-110 (or PG110) are in earlier stages (9). Nonetheless, a search of clinicaltrials.gov suggested that only tanezumab was in active trials for OA as of August 2016. Each of these agents likely has substantial efficacy in palliating OA pain. Although they have been tested in a variety of other painful conditions, including chronic lower back pain and neuropathic pain (10), it appears that they have their greatest effect in OA pain.

Efficacy

Two recent systematic reviews have each confirmed that inhibition of NGF through targeted monoclonal antibody therapy effectively relieves pain and improves function in OA. Schnitzer and Marks reviewed the efficacy of all three anti-NGF agents in clinical development (11) whereas Kan *et al.* restricted their analysis to the use of tanezumab in OA of the knee (12). The former identified thirteen multicenter placebo-controlled trials of OA

of the hip or knee that met their inclusion criteria, including an unpublished study that had been presented in abstract form (since published (13)), whereas the latter identified only four studies of tanezumab in knee OA that met their inclusion criteria. All studies in both reviews were funded by the pharmaceutical industry. The conclusions of each review, however, were similar: compared to placebo, NGF inhibition yielded substantial pain improvement, with standardized mean differences in the 0.35–0.5 range. Moreover, function, as assessed by the WOMAC function subscale, was also improved. In studies of tanezumab monotherapy compared with either NSAIDs or with opiates, tanezumab in doses of 5 mg and 10 mg were statistically significantly superior to the active comparators, with standardized effect sizes of 0.22 to 0.24 (11, 14).

Risks

While anti-NGF therapy has been shown to be efficacious in OA, safety concerns led to the US FDA hold on all clinical testing in 2010. These were based on reports of rapidly progressive OA and of osteonecrosis (ON) among patients who had received anti-NGF therapy, including involvement of joints without known OA. Detailed reviews of the adverse events reported during clinical trials with tanezumab and fulranumab were performed by an expert adjudication committee funded by Pfizer. A dose-response relationship was noted between the serious events (progressive OA and reported ON) and doses of tanezumab between 2.5 mg and 10 mg (15) and this has resulted in dose reductions in subsequent trials; the current maximum dose is 5 mg. Interestingly, the incidence of ON may be lower than previously thought. Of the 86 reported cases of ON, the Pfizer-funded adjudication committee could demonstrate unambiguous ON in only two (though eight had insufficient information to distinguish primary ON and the committee failed to reach consensus on another 5) (16). Importantly, the risk of developing rapidly progressive OA appeared to be significantly greater when tanezumab was used in conjunction with NSAIDs, compared to tanezumab monotherapy (15, 16). This observation has resulted in strict limits on the duration of NSAID use during exposure to anti-NGF therapy in subsequent trials.

Notwithstanding the risks, cost-effectiveness analyses suggest that the pain palliation provided by anti-NGF therapy is sufficiently significant that even a rate of rapidly progressive OA occurring in up to 10% of patients would not nullify the overall improvement in quality-adjusted life years (QALY) achieved (17), and that anti-NGF therapy could be cost effective at up to $400 per dose (17).

PRECLINICAL TESTING OF NGF BLOCKADE IN ANIMAL MODELS OF OA

In an attempt to gain a deeper understanding of the observed efficacy and adverse effects in clinical trials, we reviewed the literature on NGF blockade in preclinical OA models. While clinical trials for OA pain have been ongoing since 2008, the preclinical literature testing the effects of NGF blockade (either through neutralizing antibodies or through blockade of TrkA) in animal models of OA has lagged behind, with the majority of reports published in the past year. We identified 8 published reports in experimental models of OA: the earlier studies solely assessed the effect of NGF blockade on pain behaviors, while more recent studies measured both pain behaviors and effects on the affected joint (summarized in Table

1). For details on the OA models and pain behavior assays utilized in these studies, please see a recent review (18). In addition, two recent veterinary trials are discussed.

Preclinical Studies Analyzing Effects on Pain Behaviors

Our search identified 4 studies that assessed the effect of NGF blockade in experimental models of OA. In each case only a single pain-related behavior was analyzed in the animals (Table 1). The first report of NGF blockade in an animal model of OA examined the effect of a single systemic injection of a soluble NGF receptor fragment containing the NGF binding domain, TrkAd5, on weight-bearing deficit in the chronic phase (week 16) of the mouse destabilization of the medial meniscus (DMM) model, and reported a reversal of weight-bearing deficits that lasted for 3 days (19). In the rat mono-iodoacetate (MIA) model, a single intra-articular injection of a small molecule TrkA inhibitor (GZ389988) 7 days after induction of the model resulted in long-term reduction of weight-bearing deficits (20). Interestingly, intra-articular injection into the contralateral joint had no effect on weight-bearing in the ipsilateral limb, suggesting that intra-articular injection does not result in substantial systemic exposure, which may limit the risk of adverse effects. A first-in-human study with ascending single intra-articular doses of GZ389988 in patients with painful osteoarthritis of the knee has recently commenced (https://clinicaltrials.gov/ct2/show/NCT02424942?term=trka+and+osteoarthritis&rank=1).

Only two preclinical studies report the use of neutralizing antibodies against NGF. In the rat MIA model, a single systemic injection of an anti-NGF monoclonal antibody (mAb) shortly after model induction (day 2) was able to reverse deficits in burrowing one day later compared to saline (21); the effect of isotype control antibody was not assessed. Finally, one study reported the effect of repeated intra-articular administration of an anti-NGF antibody into the knee of *PKCδ* null mice that underwent DMM surgery (injections started two weeks after surgery, twice a week, for 6 weeks) (22). The effects of anti-NGF antibody in wild-type mice were not reported in this study. *PKCδ* null showed more severe mechanical allodynia after DMM than wild-type mice, despite less pronounced cartilage damage, and repeated intra-articular administration of anti-NGF decreased established mechanical allodynia of the hind paw compared to *PKCδ* null mice injected with saline; the effect of isotype control antibody was not assessed. It should be considered that inclusion of isotype control antibodies may be important when assessing pain-related outcomes, since immunoglobulins have well documented anti-inflammatory and potentially analgesic effects (29, 30).

Preclinical Studies Analyzing Effects on Pain Behaviors and Joint Structure

In light of the reported adverse events in clinical trials, it is clearly warranted that preclinical studies not only assess the effects on pain-related outcomes but also include assessment of the joint. In the past year, four publications evaluated effects of anti-NGF antibodies or TrkA inhibition on both pain behavior and some aspect of joint structural integrity (Table 1). A single systemic injection of an anti-NGF antibody (AS2886401-00) on day 3 after MIA induction in rats decreased gait changes by day 35, compared to vehicle; an isotype control antibody was not tested (23). Treatment caused an increase in knee diameter (day 35), but there was no effect on macroscopic tibial cartilage damage; joint histology was not performed.

Two recent papers evaluated the effect of long-term NGF blockade in rat meniscal surgery models. Nwosu *et al.* studied the effect of an oral TrkA inhibitor, AR786 (24). Prophylactic treatment (1 day prior to transection of the medial meniscus (MNX) surgery until day 28 *post* surgery) prevented development of weight-bearing asymmetry and mechanical allodynia of the hind paw, and showed a trend toward an increase in macroscopic chondropathy and microscopic synovitis by day 28, but statistics comparing the inhibitor-treated rats to vehicle-treated rats were not presented (24). Therapeutic treatment (day 14–day 21) successfully reversed weight-bearing asymmetry and mechanical allodynia of the hind paw, while no short-term effect on macroscopic chondropathy or histologic cartilage degeneration was observed (24). There was a trend toward decreased knee swelling and an increased histological calcified cartilage and subchondral bone damage score (includes subchondral bone sclerosis as well as fragmentation of calcified cartilage (24, 31)), although statistics were not presented (24).

Similar findings were recently reported using tanuzemab in a 28-day rat medial meniscal tear (MMT) model (25). LaBranche *et al.* tested the effect of prophylactic administration of tanuzemab and found a positive effect on gait deficiency 3–8 days after surgery, but this was accompanied by a significant increase in tibial cartilage degeneration, subchondral bone sclerosis, and tibial osteophytes compared to isotype control by day 28 (25). Therapeutic treatment with tanezumab, administered on days 23 and 31 *post* surgery, also increased tibial cartilage degeneration by day 37. In contrast, when onset of treatment with tanezumab was delayed to 8 weeks after MMT surgery (given on days 57 and 64), at which time joint damage was more severe and no gait deficiency was noted, there was no increase in cartilage damage by day 71.

One study evaluated the effect of the anti-NGF mAb, muMab 911, in a 28-day rat MIA model. This model is characterized by weight bearing deficit, mechanical allodynia of the hind paw, cartilage damage, synovitis and increased numbers of subchondral osteoclasts. Both prophylactic and therapeutic (injections on days 14 and day 21) treatment significantly prevented or reversed pain behavior but did not alter cartilage or synovial pathology; isotype control antibody was tested in a separate cohort and behaved similarly to vehicle (26). However, it can be noted that, as in the meniscal surgery models, that prophylactic treatment resulted in a trend toward an increase in both histological cartilage damage and synovitis scores by day 28, but statistics comparing antibody to vehicle were not presented (26). Interestingly, both preventative and therapeutic muMab 911 reduced numbers of TRAP positive osteoclasts in the subchondral bone at the tibial plateau. Similarly, Nwosu *et al.* tested the effects of the TrkA inhibitor, AR786, in the rat MIA model and found that therapeutic treatment (day 14–day 21) successfully reversed MIA-induced pain behavior (24). This was accompanied by a decrease in synovitis score and a trend toward a decrease in macroscopic chondropathy, histologic cartilage degeneration, and histologic calcified cartilage and subchondral bone damage scores by day 21.

Together, these studies support the clinical trial results in that blockade of NGF signaling is effective in treating pain associated with different stages of OA, but it may also promote more rapid cartilage degeneration, synovitis, and possibly subchondral bone changes, particularly when treatment starts in the earlier stages of disease. Chondrocytes and

synoviocytes are known to express both NGF and TrkA, particularly under pathogenic conditions (5), but the role of NGF signaling in these tissues has not been fully elucidated, and it is possible that NGF signaling within the joint may also be protective in some way. In addition, anti-NGF treatment in adult rodents has been shown to reduce the function of the sympathetic nervous system (32–35). The role of sympathetic nerves in the pathogenesis of OA remains unknown, but studies have demonstrated that there are sympathetic nerves associated with neovascularization in the area of the osteochondral junction as well as in osteophytes in OA (36, 37).

Veterinary Clinical Trials

Both cats and dogs may suffer from degenerative joint disease and associated mobility impairment. As such, there is interest in the veterinary community for novel drugs to treat this condition and as a result of the promising clinical trial data in human OA, canine and feline versions of anti-NGF antibodies have been developed. In two recent veterinary clinical pilot studies, a single systemic dose of anti-NGF mAb was able to provide analgesic relief to both dogs and cats with degenerative joint disease (27, 28). No side effects were noted, but no assessments of the joint were performed in these studies. Future trials in these communities may represent an opportunity for improving our understanding of the risks/benefits of these drugs by incorporating structural assessments.

CONCLUSIONS

There is a great deal of enthusiasm regarding the potential of anti-NGF therapy to palliate pain and improve function in patients with severely symptomatic OA. Nonetheless, it appears that the benefit carries a risk of exacerbating structural OA in several joints. The actual benefits and risks of anti-NGF therapy remain to be fully elucidated; ultimately, however, the proper balance between benefit and risk will be determined by individual patients with their physicians. Preclinical models may be useful for determining which patient populations may be best served as well as how to avoid adverse effects. To date, very few preclinical studies have tested the effects of long-term NGF blockade in experimental OA. Nonetheless, it can be anticipated that studies in experimental OA will enable researchers to address critical questions that will inform future clinical trials. These include evaluating the effects of intra-articular *vs.* systemic delivery; additional research into the effects of NGF blockade on joint structure, including non-affected joints; how these effects are dependent on the state of the joint at the start of treatment; and the effect of anti-NGF and NSAID combination treatment. Mechanistic studies are needed for improved targeting of what appears to be a key pathway in OA joint pain.

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Key points

Please include 3 to 5 key bullet points that summarise your article after the main body of text. The aim of these is to encourage others to cite your article based on the stated key points. Please ensure each bullet is no longer than one sentence.

- Anti-NGF therapy has been shown to improve pain and function in osteoarthritis patients.
- High doses of anti-NGF, and combination of anti-NGF with NSAIDs have been reported to increase the risk of rapidly progressive osteoarthritis.
- Pre-clinical studies testing NGF blockade have supported the clinical trial findings of improved pain.
- Some pre-clinical studies report increased joint damage with NGF blockade.
- Mechanisms of adverse effects are not understood, and detailed preclinical studies will be needed to elucidate them.

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Table 1

Type of Study	Model	Type of Blocker	Administration Protocol	Major Effects of Treatment	Reference
Pain Assessment only	Destabilization of the medial meniscus (DMM) surgery in wild-type mice	human soluble receptor to NGF (TrkAd5; produced by David Dawbarn, University of	single subcutaneous injection of 2 mg/kg either the day before surgery or 16 weeks after surgery	• Treatment before surgery prevented the development of weight-bearing asymmetry through day 3 post surgery • Treatment 16 weeks after surgery reversed weight-bearing asymmetry days 1-3 post treatment • Joint histology was not performed	McNamee 2010 [19]
	Rat MIA (1 mg, unilateral)	small molecule inhibitor of TrkA (GZ389988)	single intra-articular injection on day 7 after MIA induction into the ipsilateral joint (dose not stated)	• Treatment on day 7 decreased weight-bearing asymmetry for 4 weeks • As a control, a subset of rats received an injection into the contralateral knee instead, which had no effect on ipsilateral joint pain • Joint histology was not performed	Flannery 2015 [20]
	Rat MIA (3 mg, bilateral)	anti-NGF mAb (derived from monoclonal antibody (mAb) variable domains extracted from the patent application WO 2004/058184 A2 (applicant: Rinat Neuroscience Corporation))	9 mg/kg, s.c., given day 2 after MIA induction	• Treatment on day 2 reversed burrowing deficit on day 3 compared to saline • Joint histology was not performed	Bryden 2015 [21]
	DMM surgery in *PKC δ* null mice	anti-NGF-2.5S antibody (Sigma, St. Louis, MO)	30μg, intra-articular, given twice weekly from week 2 to week 8 post-DMM surgery	• Treatment decreased mechanical allodynia of the hind paw from week 3 to week 8 compared to saline-injected controls • Wild-type mice were not tested • Joint histology was not performed	Kc 2016 [22]
Pain and Joint Assessment	Rat MIA (1 mg, right knee)	anti-NGF antibody (AS2886401-00, human IgG1)	one injection (0.1, 0.3 or 1 mg/kg, i.v.)	• Treatment on day 3 decreases gait imbalances on day 35 after MIA induction (doses 0.3 and 1 mg/kg) compared to saline • Treatment on day 3 or day 14 decreased gait changes on day 21; Treatment 1 hr or 24hrs before gait testing on day 21 had no effect. • Treatment on day 3 caused increase in knee diameter on day 35; no effect on macroscopic scoring of tibial surface on day 35	Ishikawa 2015 [23]

Type of Study	Model	Type of Blocker	Administration Protocol	Major Effects of Treatment	Reference
	Rat transection of the medial meniscus (MNX)	orally active inhibitor of TrkA kinase activity (AR786)	Preventative: 30 mg/kg, orally administered twice daily beginning one day prior to MNX surgery and continuing through day 14 or day 28 after surgery	• Rats that received treatment through day 28 were protected from developing weight-bearing asymmetry and mechanical allodynia of the hind paw at all time points through day 28 • Rats that received treatment through day 14 continued to be protected from weight-bearing asymmetry on days 15, 17, and 21 and from mechanical allodynia of the hind paw on day 17; these rats developed both behavioral changes by day 28 • No statistically significant effect on macroscopic chondropathy or histological synovitis score by day 28, but trend toward increase in both protocols	Nwosu 2016 [24]
	Rat MIA (1 mg, unilateral) or rat transection of the medial meniscus (MNX)	orally active inhibitor of TrkA kinase activity (AR786)	Therapeutic: 30 mg/kg, orally administered twice daily from day 14 to day 21 after MIA induction or MNX surgery	• Treatment decreased weight-bearing asymmetry on day 17 and day 21 in MIA and on day 19 and day 21 after MNX • Treatment decreased mechanical allodynia of the hind paw days 19 and 21 for both MIA and MNX • In MIA model, treatment caused a statistically significant reduction in histological synovitis score and a trend toward a decrease in macroscopic chondropathy and histological cartilage degeneration and subchondral bone scores by day 21 • In MNX model, no effect on macroscopic chondropathy or histological cartilage degeneration scores, but trend toward decreased knee swelling and increased histological subchondral bone score by day 21	Nwosu 2016 [24]
	Rat medial meniscal tear (MMT) (right knee)	humanized anti-NGF mAb (tanezumab)	Preventative (0.1, 1, or 10 mg/kg, s.c., weekly from day of surgery through day 28 after surgery)	• Gait deficiency in MMT rats administered vehicle or isotype control (IgG2a) peaked 3 days after surgery, continued through day 7 and resolved by days 14–28 • Tanezumab protected against gait deficiency at all time points • Increased tibial cartilage degeneration at days 7, 14, 28 for all doses of Tanezumab compared to isotype controls • Increased subchondral bone sclerosis at days 7, 14, 28 for all doses • Increased tibial osteophytes by day 28 for all doses	LaBranche 2016 [25]

Type of Study	Model	Type of Blocker	Administration Protocol	Major Effects of Treatment	Reference
				• Adverse Effects: Focal areas of alopecia along the mouth/muzzle began developing on day 14 and were seen in most animals in the 1 mg/kg tanezumab group by day 28.	
	Rat MMT (right knee)	humanized anti-NGF mAb (tanezumab)	Therapeutic (0.1 mg/kg, s.c., days 23 and 30 after surgery)	• Increased tibial cartilage degeneration on day 37	LaBranche 2016 [25]
	Rat MMT (right knee)	humanized anti-NGF mAb (tanezumab)	Therapeutic (0.1 mg/kg, s.c., days 57 and 64 after surgery)	• No statistically significant increase in tibial cartilage degeneration on day 71	LaBranche 2016 [25]
	Rat MIA (1 mg, left knee)	anti-NGF mAb (muMab 911, mouse monoclonal antibody against hNGF)	Preventative (10 mg/kg, s.c., weekly from the day of MIA induction)	• Prevented weight-bearing asymmetry through day 28 compared to saline • Alleviated mechanical allodynia of the hindpaw at day 28 only • Trend in increased cartilage damage and synovitis by day 28 • Decreased number of TRAP positive osteoclasts in tibial plateau by day 28 • Adverse Effects: From Day 12 onwards of the preventative muMab 911, some rats exhibited skin irritation • Isotype control (IgG1) had no effect on weight-bearing asymmetry or mechanical allodynia compared to vehicle	Xu 2016 [26]
	Rat MIA (1 mg, left knee)	anti-NGF mAb (muMab 911, mouse monoclonal antibody against hNGF)	Therapeutic (10 mg/kg, s.c., days 14 and 21 after MIA induction)	• Decreased weight-bearing asymmetry at day 28 • Decreased mechanical allodynia at day 21 • On average, no change in cartilage damage, but half the rats had less cartilage damage and half the rats had more cartilage damage than the rats in the vehicle group • No change in synovitis by day 28 • Decreased number of TRAP positive osteoclasts in tibial plateau by day 28	Xu 2016 [26]
Veterinary pilot study	Randomized, parallel group, stratified, double masked, placebo controlled, proof of principle clinical pilot study design; dogs with	canine-specific anti-NGF mAb (NV-01)	Single dose of 200 μg/kg of a 2 mg/ml solution administered IV over a 1-minute period through an intra-venous 20G catheter	• Improvement in owner assessment criteria days 14 and 28 compared to placebo (saline) • Other outcome measures had overall improvements in the treatment group but not in the placebo group, altough there were not statistically signficant differences at any one time point	Lascelles 2015 [27]

Type of Study	Model	Type of Blocker	Administration Protocol	Major Effects of Treatment	Reference
	degenerative joint disease and mobility			• No adverse events over 4-week period	
	Placebo-controlled, pilot, masked clinical study; cats with degenerative joint disease and mobility impairment	fully felinized anti-NGF mAb (NV-02)	Single dose of 0.4 or 0.8 mg/kg, s.c.	• Improved activity levels in cats for 6 weeks • Overall, there was a strong placebo effect, but owner assessments of the treatment group improved at week 3 compared to placebo (saline) • No adverse events over 6-week period	Gruen 2016 [28]