Identification and possible pathogenesis of bedinvetmab-associated adverse joint events

Bedinvetmab (Librela; Zoetis), an anti-nerve growth factor monoclonal antibody, is widely used for analgesia in canine osteoarthritis and is generally regarded as safe. However, emerging clinical experience and pharmacovigilance data indicate rare but clinically significant adverse joint events. This article describes and characterises atypical musculoskeletal adverse effects observed in dogs treated with bedinvetmab, drawing on referral caseload experience and comparative human anti-nerve growth factor data. Two principal patterns are identified: (1) rapidly progressive joint destruction resembling rapid progressive osteoarthritis; and (2) a more insidious syndrome characterised by extensive periarticular heterotopic mineralisation, exostoses and chondro-osseous metaplasia, termed anti-nerve growth factor-induced insidious periarticular mineralisation. These changes may progress despite effective analgesia, delaying recognition and leading to severe joint compromise. Proposed mechanisms include altered joint loading, disruption of nerve growth factor mediated tissue homeostasis and impaired mesenchymal stem cell-driven repair. The article emphasises the importance of baseline and follow-up imaging, careful monitoring of clinical response and reporting of suspected adverse events. Improved awareness is essential to refine diagnosis, management and pharmacovigilance of these emerging conditions. https://doi.org/10.12968/coan.2026.0009

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Bedinvetmab (Librela; Zoetis), a monoclonal antibody for managing osteoarthritis pain in dogs, is generally thought to have a favourable safety profile (Corral et al, 2021). Recently, the Food and Drug Administration's Center for Veterinary Medicine evaluated adverse events reported in dogs treated with bedinvetmab. These events included ataxia, seizures, neurologic signs, paresis, recumbency, urinary incontinence, polyuria and polydipsia. In some cases, death or euthanasia was reported as an outcome. More recently the Veterinary Medicines Directorate (2026) have published results of in-depth assessment of selected adverse events for Librela Solution for Injection for Dogs, which references a small number of dogs being identified in which arthritis or similar problems were reported after receiving bedinvetmab, and where existing osteoarthritis seemed to worsen more quickly than would normally be expected. These cases are thought to be extremely rare, being reported in fewer than 1 in 10 000 estimated treated dogs.

Adverse events concerning the musculoskeletal system in dogs are increasingly being recognised in clinical practice (Farrell et al, 2025; Mobasheri et al, 2025), although the true incidence is currently unknown. The Food and Drug Administration put human anti-nerve growth factor mAb (aNGFmAb) development programmes on hold because of increased serious joint-related adverse events. These

included osteonecrosis and rapid progressive osteoarthritis, occurring in patients treated with tanezumab alone or with non-steroidal anti-inflammatory drugs. These events were noted in phase II and III trials, with a mean treatment duration of 199 days (Gimbel et al, 2014; Hochberg, 2015). Higher incidence of joint destruction was linked to longer exposure, larger doses and concurrent use of non-steroidal anti-inflammatory drugs (McKelvey et al, 2013; Hochberg, 2015), although serious joint issues also occurred in some patients after a single aNGFmAb treatment (Hochberg et al, 2016).

Characteristics of rapid progressive osteoarthritis in humans are rapid clinical deterioration (increase in pain) and radiographic progression of joint degeneration (Wenham et al, 2014). Although theories have been proposed, the cause of anti-nerve growth factor-related rapid progressive osteoarthritis in humans remains unclear (Flemming and Gustas-French, 2017). Overloading, resulting from increased activity and weight-bearing as a result of effective analgesia (analgesic arthropathy), immune reactions and neuropathic arthropathy (nerve damage resulting in loss of ability to feel the joint and a decrease in joint stability) have been suggested as potential factors leading to rapid progressive osteoarthritis following anti-nerve growth factor therapy (Fukui et al, 2014; Hochberg et al, 2016; LaBranche et al, 2017).

Nerve-growth factor signalling and joint homeostasis

The nerve growth factor signalling pathway is one of the major pain-conducting pathways in joints and bones, and has a significant role in chronic pain associated with osteoarthritis (Shang et al, 2017), hence the interest in therapeutic molecules to block it. In osteoarthritis, sensory nerves associated with the synovium, articular cartilage, subchondral bone and periosteum transmit pain signals in response to degenerative changes in those structures. As the disease progresses, inflammation leads to cartilage loss and subchondral bone microfractures, while nerve growth factor levels increase in the joints and sensory nerves endings, and its receptors proliferate. This leads to progressive amplification of nociceptive signals, central sensitisation and chronic pain. These pain signals are mainly transmitted by nerve growth factor binding to a receptor called tropomyosin receptor kinase A (TrkA) in sensory nerve endings. In addition to mediation of pain, nerve growth factor has an important role in cartilage and bone homeostasis (Sun et al, 2022), as well as in healing of damaged soft tissues via the TrkA signalling pathway (Micera et al, 2007; Jiang and Tuan, 2019; Chen et al, 2025). Nerve growth factor binding to TrkA has also been shown to cause the formation of abnormal mineralisation of soft tissues (heterotopic mineralisation) following trauma (Jiang et al, 2024) and nerve growth factor antagonists have been discussed as therapeutic targets to inhibit this aberrant calcification of soft tissues (Chen et al, 2025). Osteoclasts are essential for bone development, repair and remodelling, functioning primarily to resorb bone matrix. When dysfunctional or hyperactive, these cells disrupt the balance of bone turnover, leading to degenerative diseases like osteoporosis or conditions such as osteosclerosis. Nerve growth factor plays a key regulatory role in this process by binding to specific receptors on osteoclasts, directly influencing their morphology, functionality and gene expression to enhance bone matrix degradation (Xiang et al, 2024). In situations where nerve growth factor is antagonised, osteoclast production and function would be affected, and this may be a mechanism by which heterotopic mineralisation could proceed unchecked. Therefore, both elevations and relative absence of nerve growth factor could result in pathways leading to abnormal mineralisation of tissues.

Nerve growth factor also has other known receptor targets, such as p75 neurotrophin receptor (p75NTR), which mediates – usually in combination with coreceptors – complex pathways involving apoptosis, inflammatory regulation and vascular reinnervation in fracture repair (Chen et al, 2025). Nerve growth factor specifically stimulates mesenchymal stem cells through the p75NTR by driving their migration and differentiation and acts as a critical regulator of skeletal health (Zha et al, 2021). The role of nerve growth factor in joint health and homeostasis is therefore incredibly complex; further study is required to fully understand how it is involved in diseased joints. Nerve growth factor also has protective and healing effects in osteoarthritic joints via mechanisms involving endogenous mesenchymal stem cells, and blocking nerve growth factor function could therefore also have deleterious effects (Micera et al, 2007).

Increasing evidence shows that nerve growth factor plays an important role in mesenchymal stem cell survival, proliferation and differentiation (Choudhary et al, 2024). Mesenchymal stem cells can also secrete nerve growth factor, thereby influencing the behaviour of surrounding cell populations (Ghasemi et al, 2023). Nerve growth factor regulates mesenchymal stem cell function primarily through binding to its high affinity receptor, TrkA, which activates downstream signalling pathways – including Sirt1, PI3K/Akt and MAPK/Erk – known to govern mesenchymal stem cell growth and differentiation. In addition, the low affinity receptor p75NTR has emerged as a valuable surface marker for identifying mesenchymal stem cell subpopulations with enhanced proliferative, differentiation, immunomodulatory and cytokine secreting capacities across tissues (Zha et al, 2021). Mesenchymal stem cells expressing p75NTR have demonstrated superior therapeutic efficacy compared with p75NTR negative, suggesting a potential strategy for optimising mesenchymal stem cell based therapies (Zha et al, 2021).

In addition, the expression of p75NTR in the synovium of osteoarthritic joints is much higher than in normal synovial membranes, raising the possibility of bone marrow

p75NTR positive mesenchymal stem cell migration via the vascular system into arthritic joints, slowing the degenerative process in osteoarthritis (Hermida-Gómez et al, 2011). Therefore, disruption of this process by blocking nerve growth factor would likely influence stem cell migration and tissue repair (Zha et al, 2021). Stem cells are the body's repair kit and project managers of tissue healing, so interruption of function via perturbations in nerve growth factor-associated signalling could have potentially disastrous effects on joint health via a number of mechanisms (Zha et al, 2021).

Patterns of bedinvetmab-associated adverse joint pathology in dogs

In dogs, there appear to be two distinct types of potential bedinvetmab-associated joint adverse events. Firstly, a rapidly progressive joint destruction leading to instability, subluxation and potential articular fractures (Farrell et al, 2025) and secondly, a more insidious degenerative process causing extensive mineralisation of periarticular soft tissue (mineralising tendinopathy and desmopathy often involving the entheses or heterotopic mineralisation), extensive palisading osteophytosis and exostoses extending well away from the articular surface, and mineralised tissue formation within the synovium and joint (chondro-osseous metaplasia) (Armitage, 2025; Farrell et al, 2025). The former can occur even after one or two treatments, whereas the latter takes time to develop and normally occurs with more prolonged treatment with bedinvetmab (>6 months). The insidious nature of the second form of adverse drug reaction can initially be masked clinically because of the analgesic properties of the medication often leading to delayed identification of a severely compromised joint.

Bedinvetmab was launched in the UK in 2021 after receiving market authorisation from the Veterinary Medicines Directorate in November 2020. Since its release, over 34 million doses of bedinvetmab have been distributed worldwide. Since 2023, Greenside Referrals (Melrose, UK), a referral practice dedicated to the diagnosis and treatment of musculoskeletal disorders using orthobiologics and rehabilitation, has seen a dramatic occurrence of atypical radiographic signs of osteoarthritis. Patients were diagnosed as having atypical osteoarthritis after reviewing radiographs provided by the referring veterinary surgeon or taken as part of the diagnostic work up. Complete histories were reviewed to determine current and previous drug administration, trauma and surgical procedures such as elbow arthroscopy with cartilage curetting and fragmented coronoid process removal. The reviewing veterinary surgeons considered the osteoarthritis to be atypical when the following were identified on radiographs in combination:

- Extensive periarticular osteophytosis
- Exostoses extending well away from the articular surfaces/joint capsule boundary along the metaphysis and diaphysis appearing like the bony plates along the back and tail of a stegosaurus skeleton: 'stegosaurus exostoses'
- Radiopaque popcorn-like calcification of periarticular proliferative tissue because of chondro-osseous metaplasia: 'popcorn mineralisation'
- Heterotopic mineralisation (mineralising enthesopathy and/or tendinopathy/desmopathy).

Clinical and radiographic features of insidious periarticular mineralisation

Many patients that have been referred to Greenside Referrals for management of their osteoarthritis have been receiving bedinvetmab for many months or years and a high percentage of cases did not have a previous radiographic diagnosis of osteoarthritis. This makes identification more challenging, as pre-treatment radiographs to compare with and timelines for the formation of the atypical pathology are not available. Despite this, the characteristic changes seen could be considered pathognomonic in the author's opinion.

Many of the atypical presentations had evidence of osteoarthritis progression and joint degeneration that was considered to be occurring faster than would be expected from the natural progression of osteoarthritis. Also, joints previously reported as normal had been found to demonstrate severe degenerative pathology following treatment with bedinvetmab. Although the natural progression of osteoarthritis has not been defined and many factors contribute to its rate of progression, experienced clinicians are still able to identify subjective abnormalities in the rate and extent of expected degeneration. All suspected cases of adverse joint events seen by the author have been reported in detail to Zoetis and the Veterinary Medicines Directorate.

The elbow is the most affected joint identified as having aNGFmAb-induced insidious periarticular mineralisation (AIPM) at Greenside Referrals. This is likely because of the high proportion of dogs referred for osteoarthritis associated with elbow dysplasia that were unresponsive to conventional management. This atypical presentation of osteoarthritis involves abnormal production of bone in and around the joint, and seems to be a canine-specific reaction. In contrast, periarticular mineralisation and new bone formation is not a feature of rapid progressive osteoarthritis following aNGFmAb therapy in humans. Rapid progressive osteoarthritis is characterised as rapid cartilage loss and destruction of the subchondral bone, leading to joint collapse (Schmelz et al, 2019). Although rapid progressive osteoarthritis-like joint destruction can and does occur in dogs (Farrell et al, 2025), the latent AIPM form may be more prevalent than currently reported as a result of a lack of identification and inappropriate classification as end-stage osteoarthritis. *Figure 1* shows the radiographic appearance of typical end-stage elbow osteoarthritis in comparison to five examples of atypical osteoarthritis associated with AIPM affecting the elbow joints.

Exostosis is defined as benign bony proliferations arising from the cortical surface of bones and is most commonly associated with abnormal endochondral ossification or periosteal osteogenic stimulation. Acquired exostoses are frequently linked to chronic mechanical loading, repetitive strain at tendon or ligament insertions, joint instability, trauma or inflammatory conditions, all of which can stimulate periosteal new bone formation. In the appendicular skeleton, these lesions may disrupt normal joint biomechanics, alter load distribution and contribute to secondary osteoarthritis. As exostoses enlarge, they may cause clinical signs through direct impingement on adjacent soft tissues or neurovascular structures, resulting in pain, reduced range of motion, lameness and functional impairment.

Canine chondro-osseous metaplasia is an acquired pathological process characterised by the metaplastic transformation of periarticular soft tissue into disorganised islands of cartilage that subsequently undergo endochondral ossification, resulting in ectopic bone formation within or adjacent to joints. Histopathologically, the lesions consist of irregular nodules of cartilage and bone with marrow like spaces, often surrounded by dense fibrous connective tissue, confirming a metaplastic rather than neoplastic or developmental origin. *Figure 2* demonstrates the radiographic, gross morphology and histopathology of an elbow joint that developed chondro-osseous metaplasia following treatment with bedinvetmab for 18 months to control osteoarthritic pain associated with elbow dysplasia and osteoarthritis. Although pre-treatment radiographs were not available, the joint had rapidly deteriorated 12 months following commencing treatment with bedinvetmab. The aetiopathogenesis of chondro-osseous metaplasia is considered multifactorial, arising in the setting of chronic joint disease and altered local tissue homeostasis. Persistent mechanical instability, microtrauma and inflammation create a permissive environment in which resident mesenchymal stromal cells within synovium and periarticular soft tissues are driven toward aberrant chondrogenic and osteogenic differentiation rather than normal fibroblastic repair (Cho and Horvai, 2015). This process parallels mechanisms described in heterotopic mineralisation, in which inappropriate endochondral pathways are activated outside the skeletal envelope.

In addition to the elbows, the digits, carpi and hocks are increasingly becoming recognised as joints predisposed to developing AIPM. *Figure 3* shows seven different joints from different patients with examples of heterotopic mineralisation and stegosaurus-type exostoses extending well beyond the articular joint margins in several different joints where the patient had received prolonged treatment with bedinvetmab. The affected joints shown in *Figure 3* had no previously reported pathology before commencing treatment. The luxation of the central tarsal bone in the hock joint shown in *Figure 3a* occurred subsequently to the formation of heterotopic mineralisation without

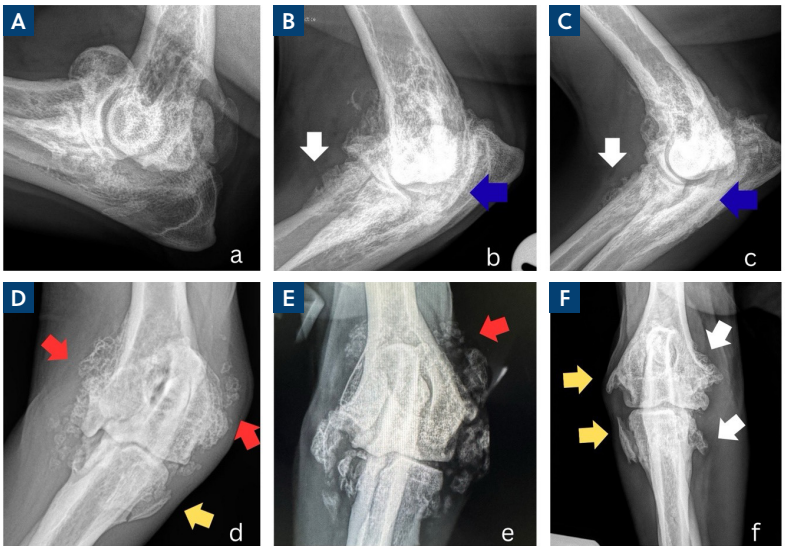

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Figure 1. Radiographs of six Labrador Retriever elbows with elbow dysplasia and osteoarthritis. A) Typical end stage osteoarthritic changes in the elbow. B–F) Atypical radiographic changes in dogs that have received greater than six monthly treatments of bedinvetmab at standard doses. White arrows indicate 'stegosaurus' exostoses, red arrows 'popcorn' mineralisation, yellow arrows heterotopic mineralisation (including mineralising enthesopathy, tendinopathy, and or desmopathy), and the blue arrows semicircular radiopacity of ulna associated with periarticular mineralisation.

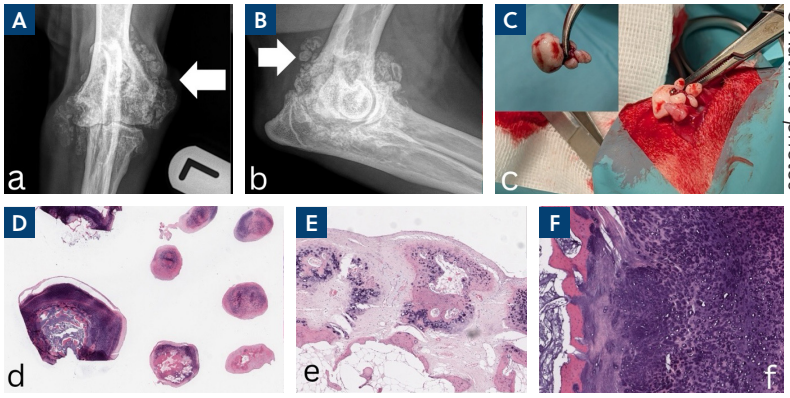

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Figure 2. A 10-year-old female neutered Labrador retriever presented for uncontrolled pain and lameness after receiving 18 doses of bedinvetmab for elbow osteoarthritis secondary to elbow dysplasia. A, B) Radiographs show severe atypical new bone formation that extends well beyond the articular surfaces that has the appearance of radio-opaque popcorn (arrow). C) An arthrotomy was performed to remove several intra-articular mobile discrete but coalescing mineralised bodies attached to the synovium by thin fibrous pedicles. D–F) Histopathology of this tissue revealed irregular nodules which consist of disorganised islands of cartilage and bone. E, F) Within the centre of the lesions, there was adipose tissue within the bone marrow spaces. There was also dense fibrous connective tissue surrounding these nodules. A histopathological diagnosis of chondro-osseous metaplasia was made.

any known trauma. In another case shown in *Figure 4*, a patient received 24 doses of bedinvetmab after radiographs revealed bilateral elbow subtrochlear sclerosis. Around 18 months later, the joints had dramatically enlarged, range of motion was severely compromised and there was marked lameness and uncontrolled pain. Increasing doses of bedinvetmab did not improve the clinical picture. Two years

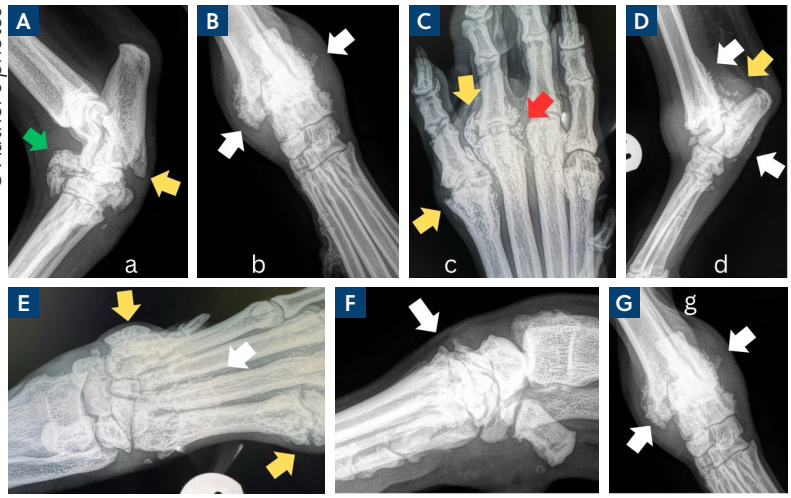

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Figure 3. Radiographs of canine joints from seven different patients exhibiting atypical osteoarthritis thought to be associated with prolonged bedinvetmab administration. In each of these examples, the joints shown were not clinically affected by osteoarthritis when treatment with bedinvetmab was initiated. White arrows indicate 'stegosaurus' exostoses, red arrows 'popcorn' mineralisation, yellow arrows heterotopic mineralisation (mineralising enthesopathy, tendinopathy, and or desmopathy) and green arrow indicates central tarsal bone luxation that occurred subsequently to the formation of the heterotopic mineralisation.

after the initial radiographs, repeat radiographs revealed severe popcorn pattern intra-articular mineralisation and extensive periarticular heterotopic mineralisation. A presumptive diagnosis of chondro-osseous metaplasia as a result of prolonged nerve growth factor suppression with bedinvetmab was made, although a histopathological diagnosis was not available.

Differentiation from typical osteoarthritis and disease progression

Radiographs of osteoarthritic elbow joints in patients with underlying elbow dysplasia typically show pathology that originates and progresses in the medial compartment and around the medial epicondyle before affecting the rest of the joint (Cook and Cook, 2009). In the case of a ununited anconeal process or advancing osteoarthritis, pathology is usually seen as osteophyte development around the anconeal process and caudal epicondyles. Osteophytes tend to be smooth and angulated over the articular surfaces (*Figure 1a*). Conversely, radiographs of dysplastic elbow joints in patients receiving bedinvetmab and where the joint degeneration had increased following treatment show extensive periarticular pathology that is usually more pronounced on the lateral aspect of the joint. This usually is a consequence of extensive heterotopic mineralisation (*Figure 1def, Figure 4cf*). Heterotopic mineralisation of structures in the medial elbow can occur after surgical trauma from procedures such as elbow arthroscopy and fragmented coronoid process removal, but it is incredibly rare to see this on the lateral aspect in normal osteoarthritis progression. The pathogenesis of heterotopic mineralisation seen in AIPM could be because of traumatic (joint instability) or neurogenic factors (Sullivan et al, 2013).

Monitoring and management

In the author's opinion, patients on long term (>6 months) aNGFmAb therapy that show a deterioration in lameness or pain state should undergo further imaging before any dose increase or dosing frequency reductions are considered. The formation of anti-drug antibodies with repeat dosing could potentially explain the lack of efficacy in some cases after prolonged treatment with aNGFmAb therapy; however, lack of efficacy should be considered an adverse drug reaction and be reported and investigated. Lack of efficacy has been one of the most reported adverse drug reactions (Monteiro et al, 2025), and further diagnostic imaging should be considered to rule out AIPM and reassess the original diagnosis. Pretreatment radiographs should be considered standard practice, not only to confirm the diagnosis of osteoarthritis, but also to be reviewed to monitor for atypical changes or speed of progression.

As part of the physical examination, joint range of motion measurements could be used to monitor changes in total range of motion over time. Goniometry is a simple and inexpensive technique that can be used to monitor mobility of all limb joints and measure change where therapeutic intervention has occurred (Armitage et al, 2023; Volz et al, 2025). A significant reduction (>6°) in either joint flexion or extension angles could indicate early joint instability or the formation of heterotopic mineralisation and/or atypical exostoses reducing range of motion. This would warrant further imaging to determine the cause and differentiate from normal progression of osteoarthritis.

Management of joints affected by AIPM is very different to joints with anti-NGFmAb reactions involving joint collapse and/or fracture. In the latter, surgical intervention is usually attempted, although some progress and require limb amputation or euthanasia (Lee and Fox, 2026). In cases of AIPM, discontinuation of bedinvetmab is warranted, but this requires substitutional analgesia and therapies to control the pain and the deleterious effects on mobility. Discontinuation of bedinvetmab does not appear to reverse the periarticular mineralisation, so additional therapies have been trialled using extracorporeal shockwave therapy and orthobiologics with some early success for mineralising tendinopathy/desmopathy and pain (author's experience). Autologous stem cell therapy in combination with platelet-rich plasma has been shown to reverse mineralising tendinopathy and enthesopathy of canine supraspinatus tendons as a result of chronic repetitive strain, as well as provide long-term amelioration of pain and increased mobility and health-related quality of life in osteoarthritis (Armitage et al, 2023). Extracorporeal shockwave therapy is beneficial in bone healing, tendon and ligament pathologies, osteoarthritis and in abnormal tissue mineralisation in humans and animals (Haupt, 1997; Boström et al, 2022; Klein et al, 2026). Using these

two modalities in combination could provide additional analgesia and have a disease modifying effect in cases of AIPM, but further exploration and research is required to demonstrate long term treatment effects. Although the pathogenesis of AIPM and osteoarthritis differ, both conditions affect joint mobility, intra-articular health, pain and health-related quality of life. Therefore, the multimodal treatment approach to osteoarthritis should be applied for AIPM. This may also involve surgical removal of intra-articular pathology such as chondro-osseous metaplasia as shown in *Figure 2* to improve joint range of motion and comfort.

Conclusions

The incidence of atypical osteoarthritis presenting at Greenside Referrals has dramatically increased in the last three years. All patients where radiographs had evidence of severe osteoarthritis with other features not commonly associated with typical disease progression were found to have received multiple treatments with bedinvetmab. Although in many cases the deterioration in joints occurred rapidly, the human medical term rapid progressive osteoarthritis does not describe the changes seen in these canine patients, and a new descriptor is required. Awareness and identification of this phenomenon will enable reporting of this adverse effect and define true incidence of occurrence. Further studies and improved pharmacovigilance are required to determine causal factors, histopathological changes in the tissues, prevalence and predisposing factors. CA

Conflicts of interest

The author declares that there are no conflicts of interest.

KEY POINTS

- Bedinvetmab is associated with rare but significant adverse joint pathology in dogs.
- Two patterns are recognised: rapid joint destruction and insidious periarticular mineralisation.
- Analgesia may mask disease progression, delaying diagnosis.
- Nerve growth factor blockade may disrupt joint homeostasis and tissue repair mechanisms.
- Baseline and serial imaging are critical for early detection and monitoring.
- Awareness and reporting are essential to accurately define incidence and risk factors.

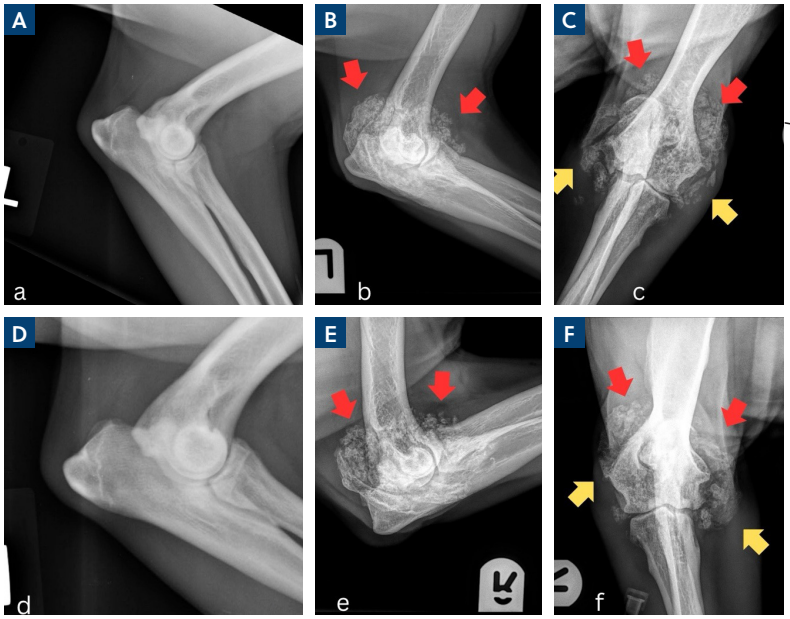

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Figure 4. A 4-year-old female neutered Labrador received 24 doses of bedinvetmab as a monotherapy after radiographs (A, D) revealed bilateral elbow subtrochlear sclerosis. Around 18 months later, the joints had dramatically enlarged, range of motion was severely compromised, there was marked lameness and uncontrolled pain. Increasing doses of bedinvetmab did not improve the clinical picture. B, C, E, F) Two years after the initial radiographs, repeat radiographs revealed severe popcorn intraarticular mineralisation and extensive periarticular heterotopic mineralisation. A presumptive diagnosis of chondro-osseous metaplasia. Red arrows indicate 'popcorn' mineralisation, yellow arrows heterotopic mineralisation (mineralising enthesopathy, tendinopathy and/or desmopathy).

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