Knee osteonecrosis incidence from two real-world data sources

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ABSTRACT

Background: Anti-nerve growth factor (NGF) has shown promise for osteoarthritis (OA) pain efficacy, but an unanticipated joint safety signal occurred in trials. To what extent this was related to OA natural history, or was a consequence of anti-NGF agents is unclear. Of the adverse joint safety events identified, osteonecrosis has specific diagnostic codes available in the medical record to enable assessment of its frequency in the general community. We therefore investigated the rates of knee osteonecrosis in three real-world cohorts using two data sources to place these trial data in context.

Methods: We used data from UK-based IQVIA Medical Research Data (IMRD) of adults diagnosed with incident knee OA between 2000 and 2018 to examine the incidence of knee osteonecrosis using different definitions. Additionally, we evaluated the incidence of knee osteonecrosis in the year prior to knee replacement in IMRD and among US Medicare beneficiaries who received a knee replacement in 2011–2014.

Results: In IMRD, among 122,343 subjects with incident knee OA (mean age 68 years, 58% female), incidence estimates for knee osteonecrosis were 0.006–0.10%, with incidence rates of 0.01–0.17 per 1000 person-years. Among the 81,807 who had a knee replacement, the incidence of knee osteonecrosis in the year prior to knee replacement was 0.004–0.06%. In Medicare, among 316,593 with knee replacement (mean age 74, 68% female), the incidence of knee osteonecrosis was 0.24–0.7%.

Conclusion: Knee osteonecrosis is rare among people with knee OA, including in the year prior to knee replacement. These data provide context for interpreting osteonecrosis events in NGF trials.

1. Introduction

Nerve growth factor (NGF) has become an attractive novel therapeutic target for the management of osteoarthritis (OA)-related pain. However, in clinical trials of anti-NGF monoclonal antibodies for symptomatic knee and hip OA, there have been reports of osteonecrosis (ON) and other joint safety events, with some participants requiring joint replacement [1,2]. While rapidly progressive OA has received much attention as an important adverse event in these trials, this entity has no specific diagnostic codes to enable evaluation of its occurrence in the general community of individuals with knee OA. In contrast, ON has specific diagnostic codes which enables assessment of its prevalence in the community, thereby providing context for interpreting the anti-NGF reports of ON.

ON occurs due to interruption of the vascular supply leading to death of bone, and is associated with pain, joint destruction, and disability [3]. The most common sites of involvement are the hip, followed by the knee. OA is a risk factor for the development of ON, including spontaneous ON of the knee (SPONK). It is unclear whether reported rates of ON of the knee on anti-NGF agents are higher than would be expected in the natural history of knee OA. There is a dearth of information regarding knee ON in the general population, in contrast to hip ON. For example, in a Japanese population-based study, the mean age-adjusted incidence rate of hip ON was 2.51 per 100,000 person-years [4].

A partial clinical hold was initially imposed by the FDA for all NGF antibody programs in 2010 due to investigator-reported ON leading to joint replacement, with resumption of the programs permitted after 2015. In the trials performed prior to 2015, the investigator-reported
rates of ON of any anatomic site in trials for tanezumab ranged from 9 to 24 per 1000 person-years for participants in active treatment arms, with an adjudicated prevalence of 0.02% [1,5]. There were no cases of ON reported in the placebo arms. During the same time period, none of the joint replacements or joint-related adverse events for those treated with fasinumab or fulranumab were adjudicated as ON [1,6].

Given the paucity of data available regarding knee ON in the natural history of knee OA, we aimed to determine the incidence of ON of the knee among those with knee OA using three real-world cohorts drawn from two large databases to provide context regarding the ON events reported in the anti-NGF trials.

2. Method

2.1. Data sources

We used two real-world data sources for our study. IQVIA Medical Research Data (IMRD) is a United Kingdom (UK) database of electronic medical records systematically and prospectively recorded data collected by general practitioner (GPs) on over 14 million individuals, including demographic factors, diagnoses (Read codes), referrals, hospitalizations, laboratory testing and prescriptions. The second data source was US Medicare (Parts A/B/D) claims data, which includes medical procedures, diagnostic codes and prescription dispensing data. Medicare is a federally funded program and provides health care coverage for nearly all legal US residents age ≥65 and some disabled patients younger than 65. The analyses using IMRD data were approved by the IRB of Boston University Medical Center, and those using Medicare data were approved by the Institutional Review Board of the Brigham and Women’s Hospital (2016P001852).

2.2. Study design

To estimate incidence of knee ON among individuals with knee OA, we conducted separate analyses within three cohorts drawn from two databases (Fig. 1).

We used data from IMRD and identified adults aged 50–89 years during 2000–2018 who were enrolled with their GP for at least one year. Eligible subjects were diagnosed with incident knee OA using one or more Read codes. To estimate the incidence of ON of the knee, we identified those among this sample who subsequently had an incident diagnosis of knee ON, identified by Read codes for avascular necrosis of the medial or lateral femoral condyle, or osteochondritis dissecans of the knee, patella, or lateral femoral condyle (knee ON-specific codes). To capture potentially additional cases of knee ON, we identified those who had a nonspecific ON code without an anatomic site coded (unspecified ON codes). These codes included avascular necrosis of other bone, idiopathic aseptic necrosis, osteochondritis dissecans, and osteonecrosis due to drugs or previous trauma.

Since ON can be an indication for knee replacement, the diagnosis of ON may be better captured in the time period prior to this procedure, and may better reflect the patients enrolled in the anti-NGF trials. We therefore identified a separate knee replacement cohort from IMRD. Because IMRD does not include codes from consultants such as orthopedic surgery, ON diagnoses may still be underestimated in this population. Thus we identified a cohort from Medicare claims data to evaluate the incidence of knee and unspecified ON in the year prior to knee replacement in those who were aged ≥65 who had received a primary knee replacement between 2011 and 2014. We identified knee ON based upon the ICD-9 code 733.43 representing “aseptic necrosis of medial femoral condyle” and ON of an unspecified site based upon the ICD-9 codes 733.40 ("aseptic necrosis of bone, site unspecified"), 733.49 ("aseptic necrosis of bone, other"), and 732.7 ("osteochondritis dissecans") (knee ON-specific code selection).

Finally, as codes for ON have not been previously validated for the identification of knee ON, we reviewed profiles of random subjects from the IMRD incident knee OA (n = 30) and KR cohorts (n = 30) who had codes for ON of an unspecified site. Profiles for each subject included clinical information up to four years before, and one year following, the first ON code. The determination of whether the ON code referred to the knee, hip, or other/uncertain site was determined based upon the proximity to other codes and available comments within unstructured data fields.

2.3. Statistical analysis

We calculated incidence of ON by dividing number of incident cases by the total of included subjects. We calculated incidence rates (IR) of knee or unspecified ON for the IMRD cohort of incident knee OA by dividing the number of cases by the person-years of follow-up. Follow-up time started on the date of first knee OA diagnosis after study entry criteria were met, and ended when a subject had the outcome of interest, died, or transferred out of a practice participating in IMRD. We also calculated the incidence of ON in the year prior to knee replacement in

Fig. 1. Study design using two databases (IMRD and Medicare) for the creation of three cohorts to study incidence of knee ON using knee ON-specific and unspecified ON code selections. A) An incident knee OA cohort was constructed from IMRD and followed for the outcome of knee ON defined by (1) knee ON-specific (2) unspecified ON code selections. B) A cohort of patients who had knee replacement from IMRD were reviewed for knee ON in the prior year as defined by (1) knee ON-specific (2) unspecified ON code selections. C) A cohort of patients who had knee replacement from Medicare were reviewed for knee ON in the prior year as defined by (1) knee ON-specific (2) unspecified ON code selections. Abbreviations: IMRD, IQVIA Medical Records Data; OA, osteoarthritis; ON, osteonecrosis.
IMRD and in Medicare beneficiaries. Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

3. Results

We identified 122,343 people from IMRD with incident knee OA, of whom 58% were female and the mean age was 68 years (Table 1). In IMRD we additionally identified 81,807 people who underwent a knee replacement (57% female, mean age 70 years). In Medicare, we identified 316,593 people who underwent a primary total knee replacement. Overall, 68% were female with a mean age of 74 years. The Medicare knee replacement cohort, overall, had a higher prevalence of comorbidities than either IMRD cohort. Bisphosphonate use was low (<10%) and any opioid use was common in all cohorts.

In the IMRD incident knee OA cohort, seven individuals (mean age 71.8, range 57–89 years) had a specific code for knee ON after knee OA diagnosis (incidence 0.006%), while 121 (mean age 68.0, range 50–89 years) had either a specific knee ON code or an unspecified ON code (incidence 0.10%). The IR was 0.01 per 1000 person-years for knee ON and 0.17 per 1000 person-years for knee or unspecified ON, over a mean follow-up time of 5.9 years.

In the IMRD knee replacement cohort, three had a code for knee ON (mean age 68.0, range 59–75 years) in the year prior to knee replacement (incidence 0.004%), and 49 had either a code for ON of the knee or an unspecified site (mean age 70.8, range 50–89 years; incidence 0.06%). In the Medicare knee replacement cohort, 775 had a code for knee ON (mean age 74.0, range 65–97 years; incidence 0.24%) and 2252 had a knee or unspecified code for ON (mean age 74.4, range 65–94 years; incidence 0.7%) in the year prior to surgery.

Table 1

| Characteristics of included subjects for the incident knee OA and KR cohorts. |
|-----------------------------|-----------------------------|-----------------------------|
| Incident knee OA cohort     | Knee replacement cohorts   |
| IMRD n – 122,343           | IMRD n – 81,807            |
| Medicare n – 316,593        |
| Age, years                  | 68.4 ± 9.9                 | 69.9 ± 8.7                  | 73.9 ± 5.8 |
| Female                      | 56.0                       | 57.0                       | 67.8 |
| White race                  | n/a                        | n/a                        | 90.4 |
| Comorbidities               |                            |                            |
| Coronary heart disease a    | 13.6                       | 9.0                        | 10.6 |
| Heart failure               | 3.6                        | 2.8                        | 8.9  |
| Hypertension                | 47.7                       | 54.1                       | 84.3 |
| Obesity                     | 37.2                       | 41.3                       | 17.1 |
| Smoking, current            | 11.1                       | 8.2                        | 12.8 |
| Type 2 diabetes             | 11.2                       | 11.3                       | 31.7 |
| Chronic kidney disease      | 8.5                        | 9.0                        | 10.8 |
| High-risk malignancy b      | 10.7                       | 11.2                       | 19.0 |
| Osteoporosis                | 6.5                        | 7.0                        | 14.6 |
| Medications                 |                            |                            |
| NSAID use                   | 38.1                       | 50.3                       | 38.4 |
| Opioid use                  | 42.6                       | 62.7                       | 58.2 |
| Corticosteroid use          | 6.9                        | 62.7                       | 35.6 |
| Bisphosphonate use          | 4.6                        | 5.7                        | 7.2  |
| Healthcare utilization      |                            |                            |
| Intra-articular corticosteroid injection received | 5.3 | 9.9 | 65.1 |
| PT referral received        | 4.4                        | 4.3                        | 21.5 |
| Emergency department visits | 0.0 ± 0.2                  | 0.0 ± 0.2                  | 0.4 ± 1 |
| Hospitalizations            | 0.2 ± 0.6                  | 0.3 ± 0.7                  | 0.2 ± 0.6 |

Continuous and count variables reported as mean ± standard deviation, and categorical variables reported as proportions.

Abbreviations: IMRD, IQVIA Medical Records Data; OA, osteoarthritis; ON, osteonecrosis; KR, knee replacement; PT, physical therapy.

a Race is infrequently recorded in IMRD and thus not included.

b Coronary heart disease includes myocardial infarction, angina, and history of coronary bypass grafting or revascularization; in IMRD, this category includes codes for ischemic or atherosclerotic heart disease.

c High-risk malignancy includes malignant neoplasms except for skin cancers in situ.

On review of 30 random subject profiles with ON of an unspecified site in the IMRD incident knee OA cohort, nine had knee ON and nine had hip ON; the rest could not be determined. In a similar review of 30 random subject profiles in the IMRD knee replacement cohort, 24 were determined to have knee ON.

A summary of ON incidence data from our three cohorts, as well as data published from the NGF programs before and after the FDA hold [1,2,5,6,8,9], are provided in Table 2.

4. Discussion

The occurrence of diagnosed ON of the knee was infrequent among people with knee OA in three separate, real-world cohorts from the US and UK, including in the year prior to knee replacement. Overall, these rates were similar to those reported in the clinical trial experience with the anti-NGF agents in the active treatment arms both before and after the FDA hold. A small numerical difference remained between the treatment and placebo arms with risk mitigation strategies in place in one program, which, in the context of other joint safety events for this class of agents across all programs, requires further examination about potential causality and mechanisms.

NGF is a neurotrophin that plays an important role in pain by sensitizing peripheral nociceptors after injury or inflammation [11]. Tanezumab, fasinumab, and fulranumab are monoclonal antibodies that specifically inhibit the interaction of NGF with its receptors, with demonstrated symptom efficacy for knee and hip OA [12]. However, unanticipated joint-related safety signals from these RCTs included investigator-reported cases of ON, rapidly progressive OA, subchondral insufficiency fracture, and the need for total joint replacement [1,2]. In light of these adverse events, the FDA placed a partial clinical hold in 2010 on studies of anti-NGF agents. Hochberg et al. published the findings of an Adjudication Committee review of 249 of 386 adverse events of either ON and/or need for a total joint replacement from phase II and

Table 2

| Data source                  | Cohort                     | Incidence estimates |
|------------------------------|----------------------------|---------------------|
|                              | Knee ON                    | knee ON or Unspecified ON |
| IMRD                         | Incident knee OA           | 0.006%              | 0.10% |
| IMRD                         | KR                         | 0.004%              | 0.06% |
| Medicare                     | KR                         | 0.24%               | 0.7%  |
| Existing published anti NGF program data |                          | Any ON |
|                              | Pre-FDA hold               | 0.02%               | Post-FDA hold: 0.10% |
| Tanezumab trials c           | Adjudicated joint-related adverse events | – | Pre-FDA hold: 0% |
| [1, 2; 5; 9]                 |                             |                     | Post-FDA hold: 0% |
| Fulranumab trials c          | Adjudicated joint-related adverse events requiring joint replacement | – | Pre-FDA hold: 0% |
| [1, 6]                       |                             |                     | Post-FDA hold: 0% |
| Fasinumab trials c           | Adjudicated joint-related adverse events | – | Pre-FDA hold: 0% |
| [10, 13]                     |                             |                     | Post-FDA hold: 0% |

a Unspecified ON in our study cohorts include knee ON and ON of site(s) otherwise not specified.

b Adjudicated ON from the anti-NGF program includes ON of any site, including knee ON.

c The ON data in tanezumab trials pre-FDA hold includes pooled data up until 2015 and summarized by Hochberg et al. [1,2]. The ON data post-FDA hold were inclusive of three phase III trials conducted after 2015 [7–9]. The denominators include all study participants who received any formulation of tanezumab.

d The ON data from fasinumab trials includes pooled data up summarized in the 2012 FDA Center for Drug Evaluation and Research Arthritis Advisory Committee (AAC) meeting [13] (pre-FDA hold), and data reported in the phase 3 trial reported by Dakin et al. [10] (post-FDA hold).
III trials of tanezumab in hip or knee OA or chronic low back pain up to 2015 [2]. Only two cases (on tanezumab doses of 5–10 mg) out of a total of 87 investigator-reported ON events were adjudicated by the commi-
tee as being ON. For fulminumab, none of the joint replacements or other joint safety events were ultimately adjudicated as secondary to ON [1,6]. At the time of FDA review in 2012, two completed fasinumab studies reported 14 joint replacements, with no cases of ON noted in the adju-
dication process [13].

Since the FDA hold was lifted after 2015, several trials have been conducted following risk-mitigation strategies (more stringent inclusion criteria, restriction to lower doses of anti-NGF agents, and removal of NSAID combination therapy intervention arms) and more thorough re-
view of joint-related adverse events [7]. A pooled analysis of joint safety events from three post-FDA hold tanezumab trials reported three events adjudicated as ON; the prevalence of ON was 0.07% for the 2.5 mg dose and 0.16% for the 5 mg dose (0.10% overall for those treated on tane-
zumab) [9]. There were no adjudicated cases of ON in the nonsteroidal anti-inflammatory drug or placebo arms. Similarly, in a post-FDA hold fasinumab RCT for hip and knee OA, no cases of ON were reported out of 337 participants who received active treatment [10]. There had been concern that the lack of systematic imaging in earlier anti-NGF trials may have under-counted ON cases and underestimated the prevalence. With the inclusion of risk-mitigation strategies, but also more systematic imaging in trials conducted after 2015, the frequency of ON was higher compared to trials conducted prior to the FDA hold (0.11% versus 0.02%).

Several hypotheses have been proposed to account for ON and other joint-related adverse events noted in the anti-NGF trials. The blockade of NGF may lead to more rapid joint destruction through the modulation of the inflammatory response or other direct bone or cartilage effects. For example, the inhibition of NGF signaling through the TrkA receptor in skeletal sensory nerves impaired bone formation in response to mech-

ical loading in one mouse model [14]. It has also been hypothesized that effective analgesia from anti-NGF agents may lead to increased ac-
tivity and mechanical overloading, which could be detrimental in a deconditioned limb and which could potentially contribute to ON or rapidly progressive OA in a vulnerable joint.

Using two independent data sources, our study provides estimates for knee ON prevalence and incidence, as well as a context regarding po-
tential expected rates of ON from general community cohorts against which to compared ON-related adverse event rates from the anti-NGF clinical trials. These findings demonstrate that general community knee ON incidence and IR estimates were within the ranges seen for some, but not all, anti-NGF trial ON reports, with data being more similar to our study’s findings for the lower doses being developed, though in the context of risk mitigation strategies being in place.

Several limitations of this study must be acknowledged. There were differences in the incidence of knee ON between our two data sources. This difference may be partially explained by a greater degree of under-
coding for knee ON in IMRD, which includes codes only from GPs, and more accurate capture of this diagnosis in Medicare which includes codes from orthopedic surgery consultations prior to knee replacement. The cohorts from the two data sources also differ by baseline demographics, with the Medicare cohort being older. We did not restrict ON cases to those with concurrent OA diagnoses in the knee replacement cohorts. However, 97–98% of knee replacement surgery are performed for knee OA. Furthermore, diagnoses of ON likely only reflect symptomatic pre-
sentations, and are only made when imaging is obtained. We were not able to confirm ON diagnoses by direct radiographic review in this study. Though prior published studies have not formally validated codes for knee ON, a study using Veterans Health Administration data documented high sensitivity and specificity of diagnostic codes for ON at multiple sites, but none involved the knee and the number of ON cases was small [15]. We reviewed a random subset of subject profiles from the IMRD cohorts who had codes for ON of an unspecified site, and found that 80% of these profiles were consistent with knee ON if the ON code appeared

within a year prior to knee replacement. We did not evaluate ON of the hip in the current study since this has been previously studied in the general population [4], and instead focused on knee ON for which there are a paucity of data. We were also unable to assess the occurrence of other joint safety adverse outcomes in anti-NGF trials, such as rapidly progressive OA or subchondral insufficiency fractures, as these were not captured with diagnostic codes in the data sources that we used.

5. Conclusion

In this study using two population-based data sources, we found low frequencies of knee ON among individuals with knee OA, which were similar to some of the data reported in the anti-NGF agent arms in RCTs. However, differences between treatment and placebo arms for overall joint safety events suggest specific anti-NGF effects. Nonetheless, our results provide some data for context and interpretation of the ON findings from the anti-NGF trials. Long-term studies for other joint-
related safety signals would provide a greater understanding of poten-
tial biologic mechanisms and underlying risk factors. Such studies are needed to identify appropriate risk mitigation strategies to safely employ use of these agents if they are approved for use in the symptomatic management of knee OA.

Authorship contributions

Jean Liew contributed to (1) the design of the study and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be submitted. Seoyoung Kim contributed to (1) the conception and design of the study and interpretation of data; (2) revising the article critically for important intellectual content; (3) final approval of the version to be submitted. Christine Peloquin contributed to (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) revising the article critically for important intellectual content; (3) final approval of the version to be submitted. Tuhina Neogi contributed to (1) the conception and design of the study and interpretation of data; (2) revising the article critically for important intellectual content; (3) final approval of the version to be submitted. Joyce Lii contributed to (1) acquisition of data, or analysis and interpretation of data; (2) revising the article critically for important intellectual content; (3) final approval of the version to be submitted. Yinzhu Jin contributed to (1) acquisition of data, or analysis and interpretation of data; (2) revising the article critically for important intellectual content; (3) final approval of the version to be submitted. Tuhiina Neogi contributed to (1) the conception and design of the study and interpretation of data; (2) revising the article critically for important intellectual content; (3) final approval of the version to be submitted. Jean Liew (jwliew@bu.edu) and Tuhina Neogi (tneogi@bu.edu) take responsibility for the integrity of the work as a whole, from inception to finished article.

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Declaration of competing interest

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References

[1] M.C. Hochberg, Serious joint-related adverse events in randomized controlled trials of anti-nerve growth factor monoclonal antibodies, Osteoarthritis Cartilage 68 (2015) S18–S21, https://doi.org/10.1016/j.joca.2014.10.005.

[2] M.C. Hochberg, L.A. Tive, S.B. Abramson, E. Vignon, K.M. Verburg, C.R. West, et al., When is osteonecrosis not osteonecrosis?: adjudication of reported serious adverse joint events in the tanezumab clinical development program, Arthritis Rheum. 68 (2016) 382–391, https://doi.org/10.1002/art.39492.

[3] M.A. Mont, D.S. Hungerford, Non-traumatic avascular necrosis of the femoral head, J Bone Jt Surg 77 (1995) 459–474, https://doi.org/10.2106/00004623-199503000-00018.

[4] R. Yamaguchi, T. Yamamoto, G. Motomura, S. Ikemura, Y. Iwamoto, Incidence of nontraumatic osteonecrosis of the femoral head in the Japanese population, Arthritis Rheum. 63 (2011) 3169–3173, https://doi.org/10.1002/art.30484.

[5] Pfizer Inc. Tanezumab arthritis advisory committee briefing document. https://web.archive.org/web/20170623024623/https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisdrugsadvisorycommittee/ucm295205.pdf. (Accessed 16 December 2020).

[6] Janssen Research & Development, LLC, Advisory Committee briefing document: JNJ-42160443 (fulranumab). https://wayback.archive-it.org/7993/20170405210331/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM295204.pdf. (Accessed 16 December 2020).

[7] T.J. Schnitzer, R. Easton, S. Pang, D.J. Levinson, G. Pixton, L. Viktrup, et al., Effect of tanezumab on joint pain, physical function, and patient global assessment of osteoarthritis among patients with osteoarthritis of the hip or knee: a randomized clinical trial, J. Am. Med. Assoc. 322 (2019) 37–48, https://doi.org/10.1001/jama.2019.8044.

[8] F. Berenbaum, F.J. Blanco, A. Guermazi, K. Miki, T. Yamabe, L. Viktrup, et al., Subcutaneous tanezumab for osteoarthritis of the hip or knee: efficacy and safety results from a 24-week randomized phase III study with a 24-week follow-up period, Ann. Rheum. Dis. 79 (2020) 800–810, https://doi.org/10.1136/annrheumdis-2019-216296.

[9] J. Carrino, T. McAlindon, E. Vignon, M. Brown, A. Burr, R. Fountaine, et al., Joint safety with tanezumab: integrated analyses from randomized controlled Phase3 studies in patients with osteoarthritis [abstract], Arthritis Rheum. 72 (suppl 10) (2020), https://acrabstracts.org/abstract/joint-safety-with-tanezumab-integrated-analyses-from-randomized-controlled-phase-3-studies-in-patients-with-osteoarthritist/. (Accessed 5 December 2020).

[10] P. Dakin, S.J. DiMartino, H. Gao, J. Maloney, A.J. Kivitz, T.J. Schnitzer, et al., The Efficacy, tolerability, and joint safety of fasinumab in osteoarthritis pain: a phase IIb/III double-blind, placebo-controlled, randomized clinical trial, Arthritis Rheum. 71 (2019) 1824–1834, https://doi.org/10.1002/art.41012.

[11] M. Schmelz, P. Mantyh, A.M. Malfait, J. Farrar, T. Yaksh, L. Tive, et al., Nerve growth factor antibody for the treatment of osteoarthritis pain and chronic low-back pain: mechanism of action in the context of efficacy and safety, Pain 160 (2019) 2210, https://doi.org/10.1097/j.pain.0000000000001625.

[12] J. Chen, J. Li, R. Li, H. Wang, J. Yang, J. Xu, et al., Efficacy and safety of tanezumab on osteoarthritis knee and hip pain: a meta-analysis of randomized controlled trials, Pain Med. 18 (2017) 374–385, https://doi.org/10.1093/pm/pnw262.

[13] US Food and Drug Administration, Center for Drug Evaluation and Research Arthritis Advisory Committee (AAC) Meeting, 2012. https://wayback.archive-it.org/7993/20170404145630/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM307880.pdf. (Accessed 16 December 2020).

[14] R.E. Tomlinson, Z. Li, Z. Li, L. Minichiello, R.C. Riddle, A. Venkatesan, et al., NGF-TrkA signaling in sensory nerves is required for skeletal adaptation to mechanical loads in mice, Proc. Natl. Acad. Sci. Unit. States Am. 114 (2017) E3632–E3641, https://doi.org/10.1073/pnas.1701054114.

[15] S.C. Vlad, D.T. Felson, D.R. Miller, Can health care databases be used to identify incident cases of osteonecrosis? Arthritis Res. Ther. 11 (2009) 1–6, https://doi.org/10.1186/ar2731.