RMD Open
Rheumatic & Musculoskeletal Diseases

VIEWPOINT

Patients with osteoporosis: children of a lesser god

Giovanni Adami ,[1] Elena Tsourdi,[2] Maurizio Rossini,[1] Thomas Funck-Brentano,[3] Roland Chapurlat[4]

To cite: Adami G, Tsourdi E, Rossini M, *et al*. Patients with osteoporosis: children of a lesser god. *RMD Open* 2023;**9**:e002973. doi:10.1136/rmdopen-2022-002973

Received 28 December 2022
Accepted 27 January 2023

[1]Rheumatology Unit, Department of Medicine, University of Verona, Verona, Italy
[2]Division of Endocrinology, Diabetes, and Bone Diseases, Department of Medicine III & Center for Healthy Aging, Technical University Medical Center, Dresden, Germany
[3]BIOSCAR UMR 1132, INSERM, Université Paris Cité, Paris, France
[4]INSERM, UMR 1033, Université Claude Bernard Lyon1, Lyon, France

Correspondence to
Dr Giovanni Adami;
adami.g@yahoo.com

ABSTRACT

Osteoporosis is a common non-communicable disease with enormous societal costs. Antiosteoporosis medications have been proven efficacious in reducing the refracture rate and mortality; moreover, we have now convincing evidence about the cost-effectiveness of antiosteoporotic medications. However, albeit preventable and treatable, osteoporosis has been somehow neglected by health authorities. Drugs approval has been unnecessarily lengthy, especially when compared with other non-communicable diseases. Herein, we discuss the issue of procrastinating drug approval in osteoporosis and future implications.

OSTEOPOROSIS, A COMMON NEGLECTED COMMON NON-COMMUNICABLE DISEASE

Osteoporosis is a common disease that causes bone fragility, which ultimately leads to fracture, disability and economic costs. The Scorecard for Osteoporosis in Europe provided an updated portrait of the European situation as regards expenditures and burden related to osteoporosis.[1] Fracture incidence is projected to increase in the coming decades due to population ageing and the costs related to osteoporosis care are likely to rise accordingly.[2] Societal costs related to osteoporosis are indeed expected to grow to more than €200 billion by the end of the next decade.[1] Notwithstanding, costs for pharmacological intervention for osteoporosis have decreased from €2.1 billion in 2010 to €1.6 billion in 2019 in Europe.[1] Such great disproportion between costs linked to fracture care and costs related to antiosteoporotic medications is surprising when compared with other diseases (eg, cardiovascular diseases (CV)), whereas the clinical burden of fracture can be immense. As an example, mortality in the year following hip fracture is close to 20% and most of the survivors will suffer from severe and prolonged disability and/or will refracture within the following year.[3] A substantial proportion of the mortality occurring after fracture is due to refracture.[4 5] Alongside with the clinical burden comes the personal economic cost, which is only partially sustained by the healthcare systems and commonly falls back on caregivers and patients.[6]

Much work has been undertaken by professional societies to tackle the fracture epidemic.[7] It is worth mentioning the 'Capture the Fracture' initiative, promoted by the International Osteoporosis Foundation.[8] Many fracture liaison services have been established throughout the world to identify, treat and monitor those sustaining fragility fractures.[3] It has been demonstrated that postfracture treatment with anti-osteoporotic medications can reduce mortality and morbidity.[9 10] Nonetheless, efforts to improve the situation are still inadequate. For example, the proportion of treated women after fracture has been recently estimated at 15% in France.[5] Treatment is often discontinued in the fear of rare adverse events[11] and undertreatment is largely prevalent, especially in men and patients with secondary osteoporosis (eg, glucocorticoid-induced osteoporosis, GIOP) or comorbidities.[12 13] Glucocorticoids, for instance, are used chronically by about 1% of the general population, causing a relevant clinical concern.[14] Most guidelines recommend treating with antiresorptives when doses above 5–7.5 mg/day are used chronically, independently from bone mineral density (BMD) or prevalent fractures.[14 15] Still, less than 10% of chronic users are treated according to local or international guidelines on GIOP.[13] Counterintuitively, initiation of glucocorticoids has been associated with prolonged discontinuation of alendronate, possibly owing to a 'sick-stopper' effect (ie, discontinue medications that are deemed to be non-essential).[11] Even more disheartening is that most glucocorticoid chronic users suffer from rheumatic musculoskeletal diseases, which pose additional risk for fracture independently from glucocorticoid use and are treated by rheumatologists

who should focus on both the rheumatic disease and the bone health of their patients.[16 17]

COMPARISONS WITH OTHER NON-COMMUNICABLE DISEASES

As mentioned above, expenditures directly related to osteoporosis medications are decreasing worldwide. Such decline is not the case for other non-communicable diseases, which have similar societal costs.[18] As an immediate example: drugs for CV represent more than 25% of total direct and indirect costs,[19] while for osteoporosis the proportion is shockingly lower (less than 3%).[20] This is exemplified by the case of antiplatelet agents for the prevention of cardiovascular events. With no doubt, antiplatelet medications, given in patients at high risk of CV events, are life-saving treatments. However, the number needed to treat (NNT) for 1 year to prevent a non-fatal cardiovascular event with aspirin is far greater than the NNT for alendronate or zoledronate to prevent a hip fracture (333[21] vs 166[22] vs 90,[23] respectively). NNT is even lower when considering major osteoporotic fractures and longer treatment duration (10 years) with bisphosphonates (3.9 for alendronate and 3.2 for zoledronate[24]). Nonetheless, aspirin is largely and inappropriately overprescribed, in direct contrast with many guidelines[25] whereas more than 75% of the patients with a hip fracture will never receive an anti-osteoporosis drug.[26]

Advances in basic research have led to the development of new potential candidates for osteoporosis treatment.[27] An outstanding example comes from the discovery of sclerostin, which effects were first described in patients affected by sclerostosis, a rare skeletal disease characterised by increased bone mass and strength. Loss of function in the sclerostin gene results in pronounced bone formation, without affecting bone strength.[28] Romosozumab, a sclerostin inhibitor, has been recently approved for the treatment of postmenopausal osteoporosis. Romosozumab is the first novel treatment for osteoporosis for over a decade and has set a new standard for BMD improvement. In clinical trials, 1 year of romosozumab has been shown to increase BMD to an extent previously not obtained with antiosteoporosis treatments.[29 30] Romosozumab decreased the incidence of new vertebral fracture by 73% against placebo (in non-severe post-menopausal osteoporosis, FRActure study in postmenopausal woMen with ostEoporosis [FRAME] trial)[29] and by 37% compared with alendronate (in severe postmenopausal osteoporosis, Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk [ARCH] trial)[31] within only 1 year of treatment. The NNT with romosozumab to avoid a new vertebral fracture were 76.9 and 43.5 when compared with placebo (FRAME trial) and alendronate (ARCH trial), respectively. The incidence of cardiac ischaemic events in patients exposed to romosozumab was higher than in those on alendronate in the ARCH trial (number needed to harm: 200). In contrast, the incidence of cardiovascular events was non-different compared with placebo in the FRAME trial. Thus, romosozumab's benefit/harm profile was considered favourable[32] and the drug was approved by the Food and Drug Administration (FDA) in 2019 and by European Medicines Agency (EMA) in late 2019. Nonetheless, many European countries have struggled to identify the criteria for reimbursement of romosozumab with consequent important delays for approval and market release. France has experienced substantial delays and romosozumab is not yet reimbursed. In many other European countries, reimbursement was achieved only in 2022, in contrast to other countries (especially outside Europe) where romosozumab was reimbursed as early as 2020 (table 1). Thousands of women have missed the opportunity to be treated with romosozumab, although this drug is targeted at those women at highest risk. The reasons for such delays and discrepancies within the EU are not elucidated and raise concern.

Table 1 Differences in year of romosozumab reimbursement in European countries

Country	Date of reimbursability
Belgium	December 2021
Denmark	October 2020
England-Wales	September 2022
France	None
Germany	February 2020
Greece	October 2022
Italy	August 2022
Netherlands	March 2021
Norway	January 2022
Scotland	November 2020
Spain	October 2022
Sweden	September 2020
Switzerland	February 2022

Romosozumab represents a quintessential negative example of procrastination of the regulatory agencies. In some countries, more than 5 years elapsed from phase 3 studies completion to market authorisation. Time from data publication to European market release has been unnecessarily lengthy for most of antiosteoporotic medications (table 2). In contrast, treatments for other common non-communicable diseases have been emblems of efficiency and rapidity for full market approval. As an example, as alirocumab, a PCSK9 inhibitor, where efficacy data were published on April 2015 in the *New England Journal of Medicine*,[33] reached the European market in early October of the same year. Similarly, evolocumab and

Table 2 Time from data publication in high impact journals to approval and market release, the good and the ugly

Drug	Data published in high impact journal	Approval by FDA	Approval by EMA	Time from data publication to European market
Osteoporosis				
Teriparatide	May 2001	November 2002	June 2003	+25 months
Denosumab	August 2009	June 2010	May 2010	+21 months
Abaloparatide	August 2016	April 2017	October 2022	*
Romosozumab	October 2016	April 2019	December 2019	+38 months
Cardiovascular diseases				
Alirocumab	April 2015	July 2015	October 2015	+6 months
Evolocumab	April 2015	August 2015	August 2015	+4 months
Inclisiran	April 2020	December 2021	December 2020	+8 months
Dapaglifozin†	November 2019	May 2020	October 2020	+11 months

*Abaloparatide received positive opinion from the Committee for Medicinal Products for Human Use in October 2022, not yet commercialised in Europe.
†For the treatment of symptomatic chronic heart failure with reduced ejection fraction.

inclisiran, two other PCKS9 inhibitors, have reached the market soon after data publication.[34 35] In addition, the SGLT2 inhibitor dapagliflozin received approval for an updated indication (heart failure with reduced ejection fraction) less than a year after the phase III study data publication.[36]

IMPLICATIONS FOR THE FUTURE

Osteoporotic fracture rates are estimated to double within the next 20 years and a true societal emergency is shaping up. Yet, osteoporosis is still a neglected disease and is often thought to be ineluctable by both physicians and patients. Undertreatment is common, especially in patients with severe osteoporosis, those who would have benefited the most from treatment. When started, anti-osteoporotic medications are commonly discontinued due to the fear of rare adverse events. Moreover, the regulatory approval of novel substances will take years, which, perhaps, sheds doubt in doctors' and patients' minds. Such impediments, along with high costs of osteoporosis trials, have deterred companies to develop new medications, so there is currently no new drug in phase 2 or 3 clinical studies. Such lengthiness does not hold true for other common non-communicable diseases (eg, CV). We sincerely hope that the experience in other non-communicable diseases will serve as a model of efficiency, possibly to be also replicated for osteoporosis.

Contributors Conceptualisation: GA, ET, RC. Writing – original draft and writing – review & editing: all.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests GA declares personal fees from Theramex, Eli-Lilly, BMS, Amgen, UCB, Fresenius Kabi, Galapagos; ET declares honoraria for lectures and advisory boards from Amgen, UCB, Takeda, Kyowa Kirin and educational grants from Takeda and UCB; TF-B declares personal fees from UCB, Amgen, Theramex, IPSEN Pharma, Kyowa Kirin; MR declares personal fees from Amgen, ABBvie, BMS, Eli Lilly, Galapagos, Menarini, Novartis, Sandoz, Pfizer, Theramex, UCB. RC declares personal fees from Lilly, BMS, Amgen, UCB, Galapagos, Abbvie, Mereo, Novartis.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Giovanni Adami http://orcid.org/0000-0002-8915-0755

REFERENCES

1 Kanis JA, Norton N, Harvey NC, *et al*. SCOPE 2021: a new scorecard for osteoporosis in europe. *Arch Osteoporos* 2021;16:82.
2 Adami G, Fassio A, Gatti D, *et al*. Osteoporosis in 10 years time: a glimpse into the future of osteoporosis. *Ther Adv Musculoskelet Dis* 2022;14.
3 Vranken L, de Bruin IJA, Driessen AHM, *et al*. Decreased mortality and subsequent fracture risk in patients with a major and hip fracture after the introduction of a fracture liaison service: a 3-year follow-up survey. *J Bone Miner Res* 2022;37:2025–32.
4 Legrand MA, Chapurlat R. Imminent fracture risk. *Joint Bone Spine* 2021;88:105105.
5 Roux C, Thomas T, Paccou J, *et al*. Refracture and mortality following hospitalization for severe osteoporotic fractures: the fractos study. *JBMR Plus* 2021;5:e10507.
6 Coassy A, Svedbom A, Locrelle H, *et al*. Costs of patient management over 18 months following a hip, clinical vertebral, distal forearm, or proximal humerus fragility fracture in france-results from the ICUROS study. *Osteoporos Int* 2022;33:625–35.
7 Martin J, Viprey M, Castagne B, *et al*. Interventions to improve osteoporosis care: a systematic review and meta-analysis. *Osteoporos Int* 2020;31:429–46.
8 Akesson K, Marsh D, Mitchell PJ, *et al*. Capture the fracture: a best practice framework and global campaign to break the fragility fracture cycle. *Osteoporos Int* 2013;24:2135–52.
9 Hsu Y-H, Li C-C, Liang F-W, *et al*. Reduced all-cause mortality with bisphosphonates among post-fracture osteoporosis patients: A nationwide study and systematic review. *Clin Pharmacol Ther* 2022;112:711–9.
10 Lyles KW, Colón-Emeric CS, Magaziner JS, *et al*. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007;357:1799–809.
11 Adami G, Jaleel A, Curtis JR, *et al*. Temporal trends and factors associated with bisphosphonate discontinuation and restart. *J Bone Miner Res* 2020;35:478–87.
12 Adami G, Gatti D, Rossini M, *et al*. Factors associated with referral for osteoporosis care in men: a real-life study of a nationwide dataset. *Arch Osteoporos* 2021;16:56.

13 Silverman S, Curtis J, Saag K, *et al*. International management of bone health in glucocorticoid-exposed individuals in the observational GLOW study. *Osteoporos Int* 2015;26:419–20.
14 Adami G, Saag KG. Glucocorticoid-induced osteoporosis: 2019 concise clinical review. *Osteoporos Int* 2019;30:1145–56.
15 Rossini M, Adami S, Bertoldo F, *et al*. Guidelines for the diagnosis, prevention and management of osteoporosis. *Reumatismo* 2016;68:1–39.
16 Wiebe E, Huscher D, Schaumburg D, *et al*. Optimising both disease control and glucocorticoid dosing is essential for bone protection in patients with rheumatic disease. *Ann Rheum Dis* 2022;81:1313–22.
17 Adami G. Regulation of bone mass in inflammatory diseases. best pract res clin endocrinol metab 2021. 2021:101611.
18 Piscitelli P, Iolascon G, Gimigliano F, *et al*. Incidence and costs of hip fractures compared to acute myocardial infarction in the Italian population: a 4-year survey. *Osteoporos Int* 2007;18:211–9.
19 Russell MW, Huse DM, Drowns S, *et al*. Direct medical costs of coronary artery disease in the united states 11this study was supported in part by parke-davis, a division of warner-lambert company, morris plains, new jersey, and pfizer, inc., new york, new york. *Am J Card* 1998;81:1110–5.
20 Burge R, Dawson-Hughes B, Solomon DH, *et al*. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res* 2007;22:465–75.
21 Bibbins-Domingo K, Force U. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S preventive services task force recommendation statement. *Ann Intern Med* 2016;164:836–45.
22 Papapoulos SE, Quandt SA, Liberman UA, *et al*. Meta-Analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. *Osteoporos Int* 2005;16:468–74.
23 Black DM, Delmas PD, Eastell R, *et al*. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809–22.
24 Adami S, Bertoldo F, Gatti D, *et al*. Treatment thresholds for osteoporosis and reimbursability criteria: perspectives associated with fracture risk-assessment tools. *Calcif Tissue Int* 2013;93:195–200.
25 Hira RS, Kennedy K, Nambi V, *et al*. Frequency and practice-level variation in inappropriate aspirin use for the primary prevention of cardiovascular disease. *Journal of the American College of Cardiology* 2015;65:111–21.
26 Kiebzak GM, Beinart GA, Perser K, *et al*. Undertreatment of osteoporosis in men with hip fracture. *Arch Intern Med* 2002;162:2217–22.
27 Tsourdi E, Rachner TD, Rauner M, *et al*. Denosumab for bone diseases: translating bone biology into targeted therapy. *Eur J Endocrinol* 2011;165:833–40.
28 Delgado-Calle J, Sato AY, Bellido T. Role and mechanism of action of sclerostin in bone. *Bone* 2017;96:29–37.
29 Cosman F, Crittenden DB, Adachi JD, *et al*. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med* 2016;375:1532–43.
30 Cosman F, Crittenden DB, Ferrari S, *et al*. Frame study: the foundation effect of building bone with 1 year of romosozumab leads to continued lower fracture risk after transition to denosumab. *J Bone Miner Res* 2018;33:1219–26.
31 Saag KG, Petersen J, Brandi ML, *et al*. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med* 2017;377:1417–27.
32 Adami G, Saag KG, Chapurlat RD, *et al*. Balancing benefits and risks in the era of biologics. *Ther Adv Musculoskelet Dis* 2019;11.
33 Robinson JG, Farnier M, Krempf M, *et al*. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1489–99.
34 Sabatine MS, Giugliano RP, Wiviott SD, *et al*. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1500–9.
35 Ray KK, Wright RS, Kallend D, *et al*. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med* 2020;382:1507–19.
36 McMurray JJV, Solomon SD, Inzucchi SE, *et al*. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;381:1995–2008.