Patients with osteoporosis: children of a lesser god

Giovanni Adami,1 Elena Tsourdi,2 Maurizio Rossini,1 Thomas Funck-Brentano,3 Roland Chapurlat4

ABSTRACT

Osteoporosis is a common non-communicable disease with enormous societal costs. Antiosteoporosis medications have been proven efficacious in reducing the fracture rate and mortality; moreover, we have now convincing evidence about the cost-effectiveness of antiosteoporotic medications. However, albeit preventable and treatable, osteoporosis has somehow been 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 events11 and undertreatment is largely prevalent, especially in men and patients with secondary osteoporosis (eg, glucocorticoid-induced osteoporosis, GIOP) or comorbidities.2 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 (33321 vs 16622 vs 90,23 respectively). NNT for alendronate or zoledronate to prevent a hip fracture (NNT) for 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 favourable32 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.

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, 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>
<thead>
<tr>
<th>Country</th>
<th>Date of reimbursability</th>
</tr>
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<tbody>
<tr>
<td>Belgium</td>
<td>December 2021</td>
</tr>
<tr>
<td>Denmark</td>
<td>October 2020</td>
</tr>
<tr>
<td>England-Wales</td>
<td>September 2022</td>
</tr>
<tr>
<td>France</td>
<td>None</td>
</tr>
<tr>
<td>Germany</td>
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<tr>
<td>Greece</td>
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</tr>
<tr>
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<td>March 2021</td>
</tr>
<tr>
<td>Norway</td>
<td>January 2022</td>
</tr>
<tr>
<td>Scotland</td>
<td>November 2020</td>
</tr>
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<td>Sweden</td>
<td>September 2020</td>
</tr>
<tr>
<td>Switzerland</td>
<td>February 2022</td>
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</table>
inclinisiran, two other PCKS9 inhibitors, have reached the market soon after data publication.  

In addition, the SGLT2 inhibitor dapagliflozin received approval for an updated indication (heart failure with reduced ejection fraction) less than a year after the approval for osteoporosis care in men: a real-world study of a nationwide life study of a nationwide fracture risk in patients with a major and hip fracture after the introduction of a fracture liaison service: a 3-year follow-up study. 

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

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

*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.

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, antosteoporotic medications are commonly discontinued due to the fear of rare adverse events. Moreover, the regulatory approval of novel substances will take years, due to the fear of rare adverse events. Furthermore, the cost 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.

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