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Article:

Aapro, M., Hadji, P., Santini, D. et al. (2025) Biosimilars in osteoporosis treatment: focus on denosumab. *Expert Opinion on Biological Therapy*, 25 (8). pp. 887-898. ISSN: 1471-2598

<https://doi.org/10.1080/14712598.2025.2540471>

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1 **Biosimilars in Osteoporosis Treatment: Focus on Denosumab**

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1 Article Highlights

- 2 1. Despite the availability of effective treatments, there is a significant treatment gap in
3 management of osteoporosis due to delayed diagnosis, undertreatment, and poor
4 adherence
- 5 2. Biosimilars such as biosimilar denosumab can make treatment more affordable and
6 accessible, offering effective yet less costly versions of biologic therapies
- 7 3. A patient-focused approach where doctors, nurses, and other healthcare workers work
8 together is important for management of osteoporosis
- 9 4. Healthcare providers and nurses play a vital role in educating patients and involving
10 them in decision-making, thus promoting adherence to treatment
- 11 5. Effective dental health management in osteoporosis requires collaboration between
12 healthcare providers and dentists, along with patient education to reduce the risk of
13 osteonecrosis of the jaw

14

1 Abstract

2 **Introduction:** Osteoporosis is a significant public health issue due to its associated morbidity,
3 mortality, and economic burden. Despite available effective treatments, a treatment gap
4 persists, characterized by delayed diagnosis, undertreatment, and poor adherence. Biosimilars,
5 such as biosimilars for denosumab, offer an opportunity to improve treatment accessibility and
6 affordability for osteoporosis and cancer-related bone loss.

7 **Areas covered:** This review explores the current treatment challenges in osteoporosis, the
8 potential of denosumab biosimilars in improving access and outcomes, and the necessity of a
9 multidisciplinary, patient-centered approach.

10 **Expert opinion:** The emergence of biosimilars for denosumab offers an opportunity to enhance
11 accessibility and affordability of osteoporosis treatment, as biosimilars provide effective and
12 economic versions of reference biologic therapies. A multidisciplinary approach is vital in
13 managing osteoporosis, central to which is the patient, whose preferences, values, and lifestyle
14 must guide the treatment plan. Healthcare providers play a crucial role in educating patients,
15 promoting adherence to prescribed treatments, and involving patients in their own care to
16 improve health outcomes.

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18 **Keywords:** Biosimilar, bone loss, denosumab, multidisciplinary, osteoporosis, patient
19 education, undertreatment

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1 Introduction

2 Osteoporosis – defined by low bone mass, deterioration of bone tissue structure, and disruption
3 of bone microarchitecture that heightens the risk of fractures – presents an ongoing public
4 health challenge with considerable associated morbidity, mortality, and economic burden [1].
5 Affecting millions of people worldwide, with prevalence increasing alongside the aging
6 population, osteoporosis is particularly common among postmenopausal women, men over the
7 age of 50, individuals on long-term glucocorticoid therapy, and patients undergoing antihormone
8 treatment for breast or prostate cancer [2]. Despite the availability of effective treatment options,
9 a substantial proportion of patients receive inadequate therapy and experience poor outcomes.
10 This treatment gap results from delayed diagnosis and significant undertreatment, often due to
11 economic barriers, limited access to healthcare, misinformation regarding the risk of rare
12 skeletal adverse effects of osteoporosis therapy, and insufficient patient education and
13 awareness among healthcare professionals (HCPs), which leaves many patients vulnerable to
14 fractures and associated complications [1,3,4].

15 The emergence of biosimilars in the treatment landscape for osteoporosis has created an
16 opportunity to reduce this gap. Biosimilars, having the indistinguishable protein structure, and
17 the same pharmacokinetic properties, efficacy and safety of their reference biologic medicines,
18 typically provide effective versions of approved treatments at a reduced cost [5,6]. Nevertheless,
19 while economic factors are important for access to treatment, other potential barriers include
20 lack of patient and HCP awareness of the disease and therapeutic options, lack of
21 understanding of the risk–benefit profile of treatment and misinformation about the risk of rare
22 adverse effects, inadequate screening for fracture risk, and low rates of treatment adherence,
23 which must be addressed to ensure that eligible patients can benefit from advancements in
24 osteoporosis care [7–9].

25 Effective management of osteoporosis requires a coordinated approach that involves HCPs
26 from various disciplines [10,11]. Heterogeneity of treatment pathways between healthcare
27 settings can make it difficult to determine the best targets for educational initiatives. Ensuring
28 that HCPs are well-informed about the latest developments, including the use of biosimilars, is
29 crucial for optimizing patient outcomes.

30 In this review, we aim to reduce the awareness gap and set the stage for the expected impact of
31 biosimilar denosumab on management of osteoporosis. We outline the current treatment

1 landscape and complexities of osteoporosis care, and discuss opportunities and challenges
2 associated with the use of biosimilars, focusing on denosumab. We explore the implications of a
3 multidisciplinary approach and patient-centered care for patients with osteoporosis and identify
4 educational needs among both HCPs and patients.

5 2 Undertreatment in osteoporosis

6 2.1 Burden of disease

7 Osteoporosis has a reported estimated global prevalence of 18.3%, affecting one in three
8 women and one in five men over the age of 50 years worldwide [2,12]. As the global population
9 ages, the prevalence of age-related diseases such as osteoporosis is expected to rise. The
10 burden of osteoporosis is multifaceted, encompassing clinical, economic, and social
11 dimensions. Clinically, osteoporosis leads to an increased risk of bone fractures, which are
12 associated with substantial morbidity and mortality [4,13]. In the US, the annual incidence of
13 bone fractures is projected to increase by 68% to reach 3.2 million by 2040, compared to 1.9
14 million from 2018 [14]. Economically, osteoporosis-related fractures impose a significant
15 financial burden on healthcare systems due to the costs of medical care, rehabilitation, and
16 long-term disability. Including direct and indirect costs, the annual costs of fragility fractures in
17 France, Germany, Italy, Spain, Sweden, and the United Kingdom are expected to increase by a
18 quarter between 2017 and 2030, from €37.5 billion to €47.4 billion [13,15]. Socially, osteoporosis
19 can lead to decreased mobility, loss of independence, and a reduced quality of life for
20 individuals affected along with an increased financial burden for patients and the healthcare
21 sector [16,17].

22 2.2 Overview of the management of osteoporosis

23 The ultimate goal of the management of osteoporosis is to improve bone health and reduce
24 fracture risk. Alongside lifestyle modifications, pharmacologic options include antiresorptive
25 therapies such as bisphosphonates, RANKL (receptor activator of nuclear factor-kappa B
26 ligand) inhibitor (denosumab), selective estrogen receptor modulator (raloxifene), menopausal
27 hormone therapy, parathyroid hormone analogues (teriparatide, abaloparatide), and a sclerostin
28 inhibitor (romosozumab) (**Fig. 1**) [18].

1 Osteoporosis can be caused by antihormone therapies used in the treatment of prostate and
2 breast cancer, as these medicines often result in decreased levels of hormones that are critical
3 for maintaining bone density. In men with prostate cancer, androgen deprivation therapy (ADT)
4 lowers testosterone and estrogen levels. Similarly, in postmenopausal women, treatment for
5 breast cancer with aromatase inhibitors reduces estrogen levels. These hormonal shifts disrupt
6 bone metabolism in both groups, resulting in bone fragility and a higher fracture risk [19].

7 Antiresorptive therapies can reduce fractures by 20–70% [20]. The ASBMR/BHOF (American
8 Society for Bone and Mineral Research/ Bone Health and Osteoporosis Foundation) Task Force
9 recommends tailoring treatment targets to each patient’s unique risk profile, considering factors
10 such as the specific indication for initiating treatment, prior fracture history (including timing,
11 location, number, and severity), and bone mineral density (BMD) levels at key sites including
12 the hip, femoral neck, and lumbar spine [21]. By utilizing measurable benchmarks, such as
13 BMD, fracture incidence, and biochemical markers of bone turnover, clinicians can effectively
14 apply a ‘treat-to-target’ approach, focusing on outcomes, monitoring, and reassessment in the
15 management of osteoporosis [18,21].

16 2.3 The osteoporosis treatment gap

17 Despite significant progress in understanding the pathogenesis and treatment of osteoporosis,
18 growing evidence shows that many patients who need pharmacologic treatment are either not
19 being prescribed the appropriate medications or are not adhering to their treatment regimens
20 [22]. Drivers for undertreatment include delays in diagnosis and risk assessment, poor treatment
21 adherence, lack of medical education, and variation in healthcare policies [1,23].

22 **2.3.1: Delays in diagnosis and risk assessment**

23 *Recommended priorities in screening and diagnosis*

24 The Endocrine Society along with the European Society of Endocrinology emphasizes the
25 heightened risk of subsequent fractures in patients who have already experienced a fracture.
26 Recognizing this risk, the management of osteoporosis should begin with assessing the
27 likelihood of future fractures using country-specific tools for informed decision-making [24].

28 For those at low or moderate risk, treatment should be guided by country-specific guidelines, as
29 fracture risks, treatment options, and associated costs can vary significantly across different

1 populations. For those identified as being at high or very high risk, initiation of treatment with
2 approved osteoporosis medications is a priority to help prevent further fractures. In
3 postmenopausal women, and men aged more than 50 years, with low BMD and high fracture
4 risk who are undergoing osteoporosis treatment, it is recommended to monitor BMD through
5 dual-energy X-ray absorptiometry (DXA) scans of the spine and hip every 1 to 3 years to assess
6 response to therapy [24,25].

7 *Screening needs*

8 Fracture as a warning signal of further fracture risk can be overlooked if mistakenly attributed to
9 the normal aging process [14]. There is a lack of follow-up of vertebral fractures detected by
10 radiography, despite their presence being associated with increased subsequent fracture risk
11 [14]. Fracture prevention strategies are most effective when individuals at risk are identified;
12 however, identification of patients with high risk of fracture can vary according to region-specific
13 screening policies [9,26]. These fractures are best identified by the Fracture Liaison Service
14 (FLS) [18,26]. While BMD is an important factor, incorporating additional risk factors alongside
15 bone densitometry has been shown to improve the accuracy of fracture risk prediction [8]. A
16 meta-analysis of three randomized studies – the ROSE (Risk-Stratified Osteoporosis Strategy
17 Evaluation) study [27], the SCOOP (Screening in the Community to Reduce Fractures in Older
18 Women) study [28], and the SOS (SALT Osteoporosis Study) study [26] – in the older
19 population with high fracture probability found that screening with fracture risk assessment and
20 bone densitometry, followed by anti-osteoporosis medication in primary care, significantly
21 reduced osteoporotic fractures compared with usual care. Specifically, the risk of osteoporotic
22 fractures (hazard ratio [HR]: 0.95), major osteoporotic fractures (HR: 0.91), and hip fractures
23 (HR: 0.80) were lowered with no significant all-fracture reduction [9,26].

24 For patients receiving antihormonal therapy for cancer, seven international societies published a
25 joint position paper to define risk factors for fragility fractures, screening strategies and optimal
26 timing, dosing, and duration of therapy for bone loss [29]. Data from clinical trials show that
27 antiresorptive treatment with denosumab and bisphosphonates reduces the risk of bone
28 recurrence and significantly reduces breast cancer mortality. Since osteoporosis is typically
29 asymptomatic until a fracture occurs, risk stratification to identify patients with early breast
30 cancer or non-metastatic prostate cancer, selecting appropriate therapy, and closely monitoring

1 those at risk of bone loss, are crucial steps to reduce the incidence, burden, mortality, morbidity,
2 and healthcare costs associated with the disease [29–31].

3 2.3.2 Treatment adherence and patient engagement

4 Treatment adherence, persistence, and duration substantially influence outcomes in the
5 management of osteoporosis [18,32,33]. It is estimated that 25–30% of individuals with
6 osteoporosis do not initiate their prescribed medication, and over 50% do not adhere to the
7 treatment regimen beyond the first year [18]. Patients with suboptimal adherence and
8 persistence experience a 30–50% higher incidence of fractures compared with those who follow
9 the prescribed regimen, along with increased morbidity, mortality, and healthcare costs [34]. A
10 common way to identify patients who are not adhering to medical treatment is to monitor bone
11 turnover markers. The IOF (International Osteoporosis Foundation) and ECTS (European
12 Calcified Tissue Society) have proposed the measurement of procollagen type I N-propeptide
13 (PINP) or C-terminal telopeptide (CTX) before and 3 months after starting osteoporosis
14 treatments, such as bisphosphonates, as the preferred way to identify nonadherence [33].
15 Compared with intravenous or oral bisphosphonates, 2-year persistence was found to be 1.5–2
16 times higher, and risk of discontinuation significantly lower ($P < 0.0001$) with denosumab in a
17 retrospective analysis of women with first time prescription for osteoporosis in Germany [35].
18 Significant factors contributing to treatment nonadherence include the cost of high-efficacy
19 medications such as denosumab and teriparatide; common side effects such as acute phase
20 reaction with zoledronate or gastrointestinal disturbance with oral bisphosphonates; fear and
21 overestimation of well-documented side effects such as atypical femur fractures and
22 osteonecrosis of the jaw (ONJ); and a lack of awareness about support programs; for example,
23 Own the Bone, and FLSs [18,34]. A meta-analysis found that patients receiving care through an
24 FLS program, compared with those receiving usual care or those in the control arm, had higher
25 rates of BMD testing (48.0% vs 23.5%), treatment initiation (38.0% vs 17.2%), and better
26 adherence (57.0% vs 34.1%) [36].

27 Adherence with oral bisphosphonates has been reported to range from 28–85% over 1 year,
28 and decreases further with each passing year [37]. Poor adherence is associated with an
29 increased risk of fracture [37]. When adherence to denosumab was assessed in an electronic
30 health record-based study, more than 20% of injections were administered with a delay of more

1 than 1 month. Patients with delays exhibited smaller increases in BMD at the lumbar spine and
2 total hip [38].

3 As age is a significant risk factor, osteoporosis is best managed with ongoing therapy and
4 monitoring, given that it has no cure. Bisphosphonate therapy is often discontinued after 3 to 5
5 years in a drug holiday to lower the risk of atypical femur fracture [18]. Discontinuing any
6 pharmacologic treatment can lead to a decline in BMD and increase the risk of fracture returning
7 to baseline levels or worsening further, but this is less of a problem with bisphosphonates as
8 their effect persists for some time after stopping. Switching treatments at different stages of the
9 disease – i.e. due to a nonresponse to treatment, adverse events, or the limited approved
10 duration of use for anabolic agents – can help in maintaining any experienced therapeutic
11 benefits [18,20,39]. The AACE/ACE (American Association of Clinical Endocrinologists/American
12 College of Endocrinology and Endocrine Society) 2020 guidelines, as well as the
13 recommendation of the ECTS, recommend against a drug holiday with denosumab, as stopping
14 treatment has been associated with a decline in BMD after 1 year and an increase in bone
15 turnover markers after 3 to 6 months [40–42]. We discuss this issue further in the section on
16 denosumab, section 3.2.

17 2.3.3 Healthcare policies

18 The intricacies of market access, healthcare provision, insurance, and reimbursement are
19 beyond the scope of this article, but restricted reimbursement has been reported as a significant
20 obstacle to accessibility and long-term uptake of medicines for osteoporosis [13]. Tong et al.
21 (2022) investigated the accessibility and affordability of monoclonal antibody and Fc-fusion
22 protein biologic medicines in the Asia Pacific (APAC) region between 2010 and 2020, finding
23 that by 2020, middle-income APAC countries (China, India, Indonesia, Malaysia, Philippines,
24 Thailand, and Vietnam) had fewer biologic medicines available compared with high-income
25 countries in the region (Australia, Hong Kong, Japan, Korea, New Zealand, Singapore, and
26 Taiwan). Additionally, the availability of biologics in APAC countries was lower than in
27 benchmark countries such as Canada, the United Kingdom, and the United States. The analysis
28 also revealed significant disparities in the consumption of biologic medicines, with emerging and
29 developing APAC nations using fewer biologics overall compared with both high-income APAC
30 countries and benchmark nations [23].

1 3 The advent of biosimilars in bone health

2 3.1 Introduction to biosimilars

3 Biosimilars are biologic medicines described as 'equivalent not identical' to an already approved
4 biologic 'reference' medicine; key features are detailed in **Table 1**. This distinction arises
5 because biologics (both reference and biosimilar) are made from living organisms and therefore
6 have natural variability that cannot be perfectly replicated, for example, differences in post-
7 translational modifications [5,6].

8 Benefits associated with biosimilars include increased access to biologic therapies, reduced
9 healthcare costs, and the fostering of competition and innovation within the pharmaceutical
10 industry. The introduction of biosimilars into the pharmaceutical market at the point of patent
11 expiry of the reference medicine can lead to substantial savings for patients, healthcare
12 systems, and payers, while maintaining high standards of safety and efficacy [43]. It has been
13 reported that US healthcare systems have saved 36 billion USD through the use of biosimilars
14 since the approval in 2015 of the first biosimilar, filgrastim, for patients with cancer receiving
15 chemotherapy and radiation therapy [47,48].

16 3.2 Biosimilars in bone health

17 The use of biosimilars in the management of osteoporosis can improve treatment access and
18 affordability for patients, providing a cost-effective alternative to reference biologic therapies,
19 thereby helping to address the growing demand for pharmacologic osteoporosis treatment. The
20 first approved biosimilar for osteoporosis treatment (approved in 2017) was for a biosimilar to
21 the reference medicine teriparatide, the active pharmaceutical ingredient of which is the 1–34
22 fragment of endogenous human parathyroid hormone, which has demonstrated benefits in bone
23 density and fracture prevention through the stimulation of bone formation. Teriparatide
24 biosimilars, generics, and the reference medicine are approved for the treatment of
25 osteoporosis in patients at high risk of fractures; however, they are not approved for treating
26 bone loss associated with antihormone therapy in breast and prostate cancer [49–51].

27 Unlike hormone-based teriparatide, denosumab, a biologic medicine first approved in 2010
28 [52,53], is a monoclonal antibody that exerts its effect by targeting and inhibiting RANKL, a
29 critical protein involved in the formation, function, and survival of osteoclasts, the cells
30 responsible for bone resorption. By blocking RANKL, denosumab reduces osteoclast activity,

1 thereby decreasing bone resorption and promoting an increase in BMD. This mechanism helps
2 to enhance bone strength and reduce fracture risk [49]. Thus, in the key FREEDOM study of
3 denosumab in postmenopausal osteoporosis, the relative increases in lumbar spine and total
4 hip BMD were 9.2% and 6.0%, respectively; the reduction in the risk of vertebral and hip
5 fractures was 68% and 40%, respectively [55]. In the open-label extension of FREEDOM (10
6 years of treatment), there were increases in lumbar spine and total hip BMD of 21.7% and 9.2%,
7 respectively [56].

8 Alongside its indications for osteoporosis (postmenopausal and glucocorticoid-induced) in
9 patients with high fracture risk, denosumab is also used to increase bone mass in patients at
10 high risk of fracture who are receiving hormone therapy for breast or prostate cancer [52,53].
11 Denosumab is administered subcutaneously, 60 mg every 6 months. The adverse reactions
12 associated with denosumab include severe hypocalcemia and mineral metabolism changes,
13 serious infections, and dermatologic adverse reactions [52,53]. However, most of these adverse
14 reactions are rare and denosumab is usually well tolerated [52,53]. Upon discontinuation, the
15 beneficial skeletal effects can reverse rapidly as denosumab circulates in the bloodstream,
16 binds to secreted RANKL in the extracellular fluid, and is cleared through the reticuloendothelial
17 system, with a half-life of around 26 days. This rebound in the BMD effect of denosumab is
18 termed the 'overshoot phenomenon', and is due to an increase in osteoclast activity, which can
19 lead to rapid bone loss and subsequent multiple vertebral fractures as bone turnover markers
20 not only return to baseline levels but often exceed them [57–59]. Thus, to maintain the benefits
21 achieved with denosumab therapy, it is recommended by the AACE/ACE, The Endocrine
22 Society, and ECTS that patients transition to bisphosphonates, preferably zoledronic acid
23 (intravenous), once discontinuation of denosumab is confirmed [40,42,60]. A clinical trial showed
24 some attenuation of the increase in CTX with zoledronic acid 5 mg given 6, 9, or 12 months
25 after the last dose of denosumab; there was still some loss of BMD over two years [61]. In an
26 observational study, the bone loss was less if patients were given oral bisphosphonates or
27 zoledronic acid in the three years following denosumab cessation [62]. Although most research
28 has been done with zoledronic acid, there is some clinical trial evidence that alendronate may
29 prevent any overshoot, but this has only been shown in one study (Denosumab Adherence
30 Preference Satisfaction [DAPS] study) after just 1 year of denosumab treatment [63]; we await
31 further trials on this topic. Also, we do not know whether the effect of bisphosphonates is related
32 to the duration of denosumab use, and we await further trials on this topic, too.

1 The ECTS has identified key risk factors for patients at increased risk of multiple vertebral
2 fractures following discontinuation of denosumab therapy, including the duration of treatment
3 (exceeding 3 years) and a strong BMD response to denosumab, and prior history of vertebral
4 fractures [42]. Initiating a potent bisphosphonate such as zoledronic acid upon stopping
5 denosumab and monitoring the treatment's effectiveness using bone turnover markers is
6 recommended. If bone turnover markers are unavailable, administering a second dose of
7 zoledronic acid after an additional 6 months is suggested [42].

8 Using denosumab in sequence with anabolic agents such as teriparatide, abaloparatide, and
9 romosozumab has been shown to maximize benefits for patients at very high risk of fractures
10 [64]. The IOF-ESCEO (International Osteoporosis Foundation–European Society for Clinical
11 and Economical Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases)
12 recommends using denosumab after teriparatide for patients with a very high fracture risk due to
13 osteoporosis, excluding those undergoing cancer treatments [8]. It is not recommended to follow
14 denosumab with teriparatide as any anabolic effect is attenuated [39]. The FRAME (FRActure
15 study in postmenopausal woMen with ostEoporosis) study found that starting osteoporosis
16 treatment with romosozumab significantly improves bone density and reduces fracture risk, with
17 continued benefits when transitioning to denosumab [58].

18 The first denosumab biosimilar, by Sandoz, was approved internationally in 2024, marking a
19 significant milestone in the advancement of osteoporosis care. Its indications match those of the
20 reference medicine [66,67]. As of 2025, there are currently three denosumab biosimilars that
21 have been approved both by the FDA and EMA at the time of writing (Jubbonti[®], Sandoz;
22 Ospomyv[™], Samsung; Stoboclo[®], Celltrion) and an additional biosimilar (Conexxence[®],
23 Fresenius Kabi) approved by the FDA only [68–70]. Sandoz denosumab was compared with
24 reference denosumab in postmenopausal women with osteoporosis, and the lumbar spine BMD
25 increases were similar (both 5.0% at 12 months) [71]. Samsung denosumab was compared to
26 reference denosumab in postmenopausal women with osteoporosis, and the lumbar spine BMD
27 increases were similar (5.6% and 5.3%, respectively, at 12 months) [72]. In postmenopausal
28 women with osteoporosis, Celltrion denosumab and reference denosumab produced similar
29 increases in lumbar spine BMD at 12 months (5.0% vs. 5.1%) [73]. As compared to reference
30 denosumab, there were similar changes in CTX, similar rates of hypocalcemia and anti-drug
31 antibodies, and switching from reference to biosimilar denosumab resulted in similar changes in
32 BMD [73–75]

1 As denosumab therapy becomes more economically accessible, and consequently available to
2 patients for whom it had not previously been considered, it will be important for HCPs to be
3 aware of the recommendations on management of the overshoot phenomenon. Understanding
4 that the benefits of denosumab treatment can be maintained after discontinuation by
5 transitioning patients to intravenous bisphosphonates may ensure that prescribers have
6 confidence to initiate denosumab treatment when clinically warranted.

7 3.3 Awareness of biosimilars among HCPs

8 In a systematic review exploring the factors affecting uptake of biosimilars, it was observed that
9 HCPs have limited understanding of biosimilars, and that they are more comfortable in
10 prescribing biosimilars to patients who are naïve to biologics than to those switching [7]. This
11 limited understanding may stem from confusion between biosimilars and generic medicines.
12 Biosimilars are equivalent with minor differences to the reference biologic medicine and require
13 extensive testing (including clinical trials) prior to approval to demonstrate similarity in safety
14 and efficacy, while generics are chemically identical to the original small-molecule drug and only
15 need to prove bioequivalence to the reference drug. Biosimilars are produced through complex
16 biologic processes and may exhibit slight variations in structure and function, unlike generics
17 which are exact replicas of their reference drugs [6,76]. These results signify the importance of
18 providing HCPs with evidence to increase their confidence in biosimilars, and to widen the
19 options available to patients.

20 Long-term data from the use of biosimilars, including real-world evidence on their safety and
21 effectiveness from analysis of post-marketing experience, have a role in helping HCPs to gain
22 confidence in prescribing biosimilars. Such studies might also aid in clarifying unresolved or
23 partially resolved issues, such as authorized indications, switching, and the immunogenicity of
24 biosimilars, and promote use of biosimilars in routine practice [77,78]. A review summarizing the
25 real-world safety experience for eight marketed biosimilars (adalimumab, epoetin alfa,
26 etanercept, filgrastim, infliximab, pegfilgrastim, rituximab, and somatropin) concluded that the
27 overall benefit–risk profile of each remains favorable and is consistent with the respective
28 reference biologic [66].

1 4 Multidisciplinary and patient-centered care in osteoporosis

2 Effective management of osteoporosis involves the collaboration of multiple HCPs (**Fig. 2**).
3 Each of these specialists brings unique expertise and perspectives, contributing to a
4 comprehensive care plan tailored to the individual needs of the patient [10,11,79]. Effective
5 sharing of critical patient information between primary care physicians and specialists is crucial
6 for supporting consistent care, which can lead to better patient outcomes, and increased
7 satisfaction for both providers and patients. However, this communication is often inadequate,
8 as demonstrated by a 2020 survey of 7,183 General Practitioners from 34 countries, which
9 identified issues such as limited nursing support and difficulties in specialist collaboration, with
10 significant variation across different countries [68].

11 4.1 Management of osteoporosis in patients with cancer

12 Cancer therapies can exacerbate bone loss at a rate more than seven-fold higher than that of
13 normal aging [69]. Early cancer diagnosis and a rapidly changing treatment landscape in
14 oncology have led to improved survival outcomes in patients with cancer, resulting in an
15 increased likelihood of patients experiencing long-term side effects from cancer treatments,
16 such as bone loss and fractures [29]. Managing osteoporosis in patients undergoing treatment
17 for cancer is therefore important and necessitates a multidisciplinary approach (**Fig. 2**).

18 As mentioned, cancer therapies such as chemotherapy and radiotherapy along with hormonal
19 therapy (gonadotropin-releasing hormone agonists, aromatase inhibitors, ADT), have been
20 shown to contribute to bone loss. Radiotherapy-induced bone loss primarily occurs due to direct
21 damage to the bone, whereas chemotherapy-induced bone damage alongside glucocorticoids
22 given to avoid side effects, may result from either direct targeting of the bone or indirect
23 systemic effects. Hormonal therapy for cancer targets estrogens and androgens, both of which
24 play a part in maintaining bone mass, and therefore disruption of these hormones can result in
25 bone loss [81,82].

26 Recent guidelines from an international expert panel of clinical oncologists and specialists in
27 metabolic bone disease recommend that clinicians use risk assessment tools to estimate
28 osteoporosis risks in patients treated for cancer, with BMD testing every 2 years [29,83].
29 Furthermore, the ASCO (American Society of Clinical Oncology) Clinical Practice Guideline for
30 osteoporosis in survivors of adult cancers with non-metastatic disease recommends a range of
31 non-pharmacologic interventions. These recommendations include monitoring calcium and

1 vitamin D intake, promoting a tailored exercise regimen (including balance, flexibility,
2 endurance, and strength training), and encouraging cessation of smoking and limiting alcohol
3 consumption [69].

4 Seven interdisciplinary cancer and bone societies (IOF, CABS [Cancer and Bone Society],
5 ECTS, IEG [International Expert Group for aromatase inhibitor-associated bone loss], ESCEO,
6 IMS [International Menopause Society], and SIOG [International Society for Geriatric Oncology])
7 have concluded that administering denosumab 60 mg or zoledronic acid 4 mg every 6 months
8 during adjuvant aromatase inhibitor therapy is recommended to prevent aromatase inhibitor-
9 associated bone loss in postmenopausal women. Zoledronic acid is recommended when the
10 focus is on minimizing disease recurrence, while denosumab is preferred when fracture risk is
11 the primary concern [29]. In patients on ADT, treatment with bisphosphonates or denosumab is
12 recommended [71]. The rebound phenomenon has been observed after stopping denosumab
13 given for aromatase inhibitor-induced osteoporosis [84].

14 4.2 Management of dental health in patients with osteoporosis

15 Current evidence demonstrates an association between antiresorptive therapies such as
16 bisphosphonates and denosumab, and an increased incidence of ONJ [85,86]. ONJ is a
17 condition where the jawbone becomes exposed and fails to heal for at least 8 weeks in patients
18 taking antiresorptive therapies [54]. Notably, the prevalence of ONJ is markedly higher in
19 oncology patients receiving high-dose regimens (<5%) compared with those treated for
20 osteoporosis with low-dose protocols (<0.05%) [85–87].

21 Effective management of dental health in patients with osteoporosis requires a collaboration
22 between dentists and other HCPs . Proactive communication between dentists and other
23 specialists about upcoming dental procedures is important for making collaborative decisions on
24 dosing and other preventive measures [88]. Sharing patient histories, treatment plans, and
25 monitoring protocols between HCPs can help minimize the potential oral health implications of
26 osteoporosis [86,88]. Invasive dental procedures should be considered carefully in patients
27 taking antiresorptive medications. The American Dental Association (ADA), for example,
28 recommends a thorough review of the patient's medical history and assessment of the risk of
29 ONJ during dental examinations to ensure appropriate dental care by the dentist. It is crucial to
30 address conditions that can lead to infection, such as caries, dental plaque, periodontitis, and
31 apical periodontitis, with conservative treatments to avoid further complications [86,88,89]. It is

1 important to involve and educate patients about dental risk management. The ADA
2 recommends an oral health program consisting of maintenance of good oral hygiene and
3 regular dental check-ups, which are vital for monitoring and minimizing the risk of ONJ [86].
4 Though the risk of ONJ is lower than the risk of multiple osteoporotic fractures [54], dentists
5 should remain vigilant in assessing oral health in individuals with osteoporosis. Implementing
6 screening protocols in dental settings could enhance the early identification of at-risk patients
7 [88,90]

8 4.3 Patient-centered care in osteoporosis

9 Central to any multidisciplinary treatment approach is the patient, whose preferences, values,
10 and lifestyle must guide the management plan. Taking the time to understand patient choices
11 and addressing any fears or misconceptions during the treatment selection process can improve
12 treatment adherence, and lead to better outcomes for patients [18]. Thus, patients should be
13 encouraged to share their questions and concerns about treatments, dosing schedules (daily,
14 weekly, monthly, every 6 months, or yearly), benefits, and potential side effects when reviewing
15 medication options with them [18,91]. Educating patients about osteoporosis includes advising
16 the patient and any caregivers about osteoporosis and its consequences, discussion of lifestyle
17 issues, the modification of risk factors, and importantly, compliance with their medication [18,92].

18 Furthermore, ensuring a clearer understanding of the benefits of biosimilars for patients is
19 important for treatment success and to minimize the risk of nocebo effects. A patient education
20 program that provides information on how biosimilars work, how they differ from small molecule
21 generic medicines, and how the regulatory approval process ensures safety and efficacy of
22 biosimilars, will help improve patient awareness of the benefits of biosimilars [77].

23 Specialist nurses play a pivotal role in patient education, breaking down complex medical
24 information into understandable terms, providing personalized advice, and building trusting
25 relationships with patients [94,95]. Specialist nurses educate patients on healthy lifestyles,
26 including nutrition, exercise, and smoking cessation, while promoting adherence to prescribed
27 medications and supplements. Nurses can also contribute to fall-reduction programs, assist with
28 early osteoporosis detection, and provide ongoing support to minimize recurrent fractures in
29 patients with a history of fragility fractures [96,97]. In a single center study in Taiwan, it was
30 observed that patients who received education from nurses were more than five times more
31 likely to choose out-of-pocket anti-osteoporotic therapy (mostly denosumab) than those who did

1 not receive such education [82]. Physiotherapists also have an important role in managing
2 osteoporosis through exercise prescription, therapeutic modalities, specific techniques, and
3 patient education. Appropriate treatment goals can be set after a comprehensive evaluation of
4 signs, symptoms, osteoporosis risk factors, and functional status, with the aim of preserving
5 bone mass, minimizing fall risk, enhancing posture, alleviating pain, and improving mobility and
6 physical function [99,100].

7 In a systematic review of the effectiveness of patient education for patients with osteoporosis,
8 published in 2022, 13 studies met the inclusion criteria and had covered at least two aspects
9 [85]. Six studies examined improvements in physical function, and all found a positive effect of
10 education; two of three reported improvements in psychological wellbeing, and only one of five
11 studies reported a benefit for physical comfort and disability. Effects on quality of life,
12 adherence, persistence, and knowledge of osteoporosis were inconclusive. The impact of
13 patient education in improving the management of osteoporosis is an area that requires further
14 research [85].

15 5 Conclusion

16 Osteoporosis remains a substantial public health issue, affecting the quality of life of millions of
17 individuals globally, and requiring comprehensive, effective, and affordable treatments.

18 Denosumab has a central role in the management of osteoporosis in patients at high fracture
19 risk, providing substantial long-term benefits including sustained improvements in BMD, and
20 with potential for treatment sequencing with anabolic agents. Furthermore, denosumab shows
21 strong clinical efficacy in managing cancer-related bone loss in patients with breast and prostate
22 cancer. The introduction of denosumab biosimilars presents a promising advancement in the
23 management of osteoporosis. By offering effective versions of expensive biologic therapies at a
24 lower cost, biosimilars may increase treatment accessibility and help to address the treatment
25 gap that currently exists. Economic accessibility alone, however, is not sufficient. HCPs must be
26 well-informed about the use of biosimilars to confidently prescribe them, and patients need to be
27 educated about the benefits and potential of these treatments. The collaborative effort of all
28 stakeholders – patients, clinicians, and HCPs – is imperative to advance the management of
29 osteoporosis, allowing patients at a high risk of bone fractures to receive the necessary
30 treatment to minimize bone loss, and reduce the likelihood of future fractures. By leveraging the

1 potential of denosumab biosimilars and fostering a multidisciplinary, patient-centered approach,
2 we can achieve better health outcomes and ensure optimal bone health for all.

3 6 Expert Opinion

4 Despite the availability of effective treatments, there is a significant treatment gap in
5 management of osteoporosis due to delayed diagnosis and undertreatment [1,3,4]. The
6 development of biosimilars, like biosimilar denosumab, have the potential to impact real-world
7 outcomes in treating patients with osteoporosis. These biosimilars provide effective and
8 economic versions of expensive biologic therapies, thus addressing significant economic
9 barriers and ensuring that more patients at high risk of fractures receive necessary treatment,
10 along with improving treatment adherence [46,50]. Denosumab, a monoclonal antibody targeting
11 RANKL, has improved osteoporosis treatment by reducing osteoclast activity, thereby
12 decreasing bone resorption and increasing BMD. This mechanism enhances bone strength and
13 reduces fracture risk, thus making denosumab a crucial treatment option [49]. The
14 multidisciplinary approach emphasized in the review highlights the importance of patient-
15 centered care, which can play an important role in better adherence and effectiveness [18].
16 However, the realistic implementation of these advances into clinical practice is contingent upon
17 overcoming several barriers. One major obstacle is the lack of awareness and education among
18 HCPs and patients regarding the benefits and safety of biosimilars.

19 Key areas for improvement include enhancing patient and HCP awareness through
20 comprehensive education and training programs, improving screening and diagnosis protocols,
21 and increasing treatment adherence [1]. Current screening methods may not adequately identify
22 patients at high risk of fractures, leading to delayed diagnosis and treatment. Implementing
23 more accurate and comprehensive screening tools can help in early detection and timely
24 intervention, thereby reducing the incidence of fractures and associated complications [9,26].
25 Technological advancements, such as improved bone densitometry techniques with the
26 integration of additional risk factors into fracture risk prediction models, can help overcome
27 current limitations [8]. Addressing the economic barriers through policy changes and financial
28 support programs is crucial for ensuring that patients can access these treatments.

29 Many HCPs are hesitant to prescribe biosimilars due to concerns about their efficacy and
30 potential side effects [7]. Extensive testing to demonstrate biosimilarity is necessary to ensure
31 the safety and efficacy of biosimilars. The regulatory authorities are actively working to further

1 streamline the approval process for biosimilars, aiming at facilitating quicker market access
2 while ensuring patient safety and maintaining therapeutic efficacy. The FDA recently proposed
3 removal of the requirement for switching studies between a biosimilar and its reference product,
4 provided that a robust, comprehensive analysis of available data demonstrating equivalence in
5 terms of safety, efficacy, and immunogenicity is provided [5,6,43,45]. Methodological
6 improvements in clinical trials and real-world evidence studies can provide robust data to
7 support the efficacy and safety of biosimilar treatments.

8 Specific to denosumab, exploring sequential therapies with anabolic agents, such as
9 teriparatide and romosozumab, may maximize the benefits and provide more effective solutions
10 for patients at very high risk of fractures [64]. In addition, increasing use of personalized
11 medicine, early integration of nutrition and lifestyle interventions, and advanced imaging
12 techniques can offer significant advancements in the diagnosis and management of
13 osteoporosis [18,39], thereby improving patient outcomes.

14 Proactive communication between a patient's dentist and HCPs is important for managing
15 dental issues in those receiving osteoporosis treatments such as denosumab to reduce risk for
16 ONJ. Good oral hygiene along with regular dental check-ups are also advised to minimize risk
17 [86,88]. Specialist nurses play a critical role in managing osteoporosis by educating patients in
18 healthy lifestyles, promoting adherence to medical regimens, and providing ongoing support,
19 which can lead to improved outcomes and patient satisfaction [94]. Physiotherapists similarly
20 contribute by prescribing tailored exercise programs and providing education to enhance
21 physical function and bone health [99,100]. Adherence to prescribed treatment is crucial in
22 managing osteoporosis, and regular physical activity supports treatment outcomes [18].

23 Evolution in the field of osteoporosis management through increased use of biosimilars,
24 improved patient education, and the use of personalized treatment approaches will ultimately
25 lead to better patient outcomes, reduced healthcare costs, and a standardized approach to
26 managing osteoporosis. Overall, the future of osteoporosis management looks promising, with
27 biosimilars playing a central role in advancing patient care and improving health outcomes.

28 Funding

29 Hexal AG (a Sandoz company) invited the authors to participate and had a courtesy review of
30 the final draft prior to submission, but did not contribute to drafting or development of the
31 content. Final approval of the manuscript rested solely with the authors.

1 Declaration of interest

2

3 MA is, or has been, a consultant for Amgen, Astellas, Chugai Pharmaceutical Co., Ltd., Daiichi
4 Sankyo, Genomic Health (Exact Sciences), GSK, Helsinn Healthcare SA, Knight Therapeutics
5 Inc., Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, and Vifor Pharma and has received
6 honoraria for lectures at symposia of Amgen, Astellas, Chugai Pharmaceutical Co. Ltd., Daiichi
7 Sankyo, Genomic Health (Exact Sciences), GSK, Helsinn Healthcare SA, Knight Therapeutics
8 Inc., Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, and Vifor Pharma. He has received
9 grant/research support from Amgen, Helsinn, Novartis, Pfizer, Sandoz, Vifo.

10 RE receives consultancy funding from Angitia, Atnam, AstraZeneca, Immunodiagnostic
11 Systems, Sandoz, CL Bio, Pharmacosmos, CureTeQ, Biocon, Grunenthal, Theramex; meeting
12 presentations for Alexion, Radius, UCB, and Amgen; and travel funding from Samsung and CL
13 Bio; and grant funding from Alexion, CL Bio, and Osteolabs. He is the chairman of the DSMB for
14 CureTeQ and STOPFOP.

15 PH has received consultancy funding from Angitia, Amgen, Celltrion, Fresenius, Gedeon
16 Richter, Hexal, Jenapharm, Sandoz, Stada, Theramex, and UCB; presentations for Amgen,
17 Celltrion, Fresenius, Gedeon Richter, Jenapharm, Stada, Theramex, and UCB; and travel
18 grants from Gedeon Richter, Theramex, and UCB.

19 DS has received consultancy funding from Astellas, MSD, Bayer, Amgen, Merck, Gilead,
20 Roche, Eisai, Ipsen, and Janssen.

21 RS has received consultancy funding from Alexion, Amgen, Sandoz, and UCB; speaking fees
22 from Alexion, Amgen, Blueprint, Takeda/Shire, Theramex, and UCB. He is chairman of the
23 German Osteology Society (Dachverband Osteologie, DVO).

24 Author contributions

25 MA, RE, PH, DS, and RS contributed equally to the concept and writing of the article.

26 Acknowledgments

27 Medical writing assistance during the preparation of this manuscript was provided by Anshu
28 Aggarwal, and editorial support was provided by Chiara Lee, PhD, both from Syneos Health
29 Medical Communications, and funded by Hexal AG (a Sandoz company).

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3 (**) to readers

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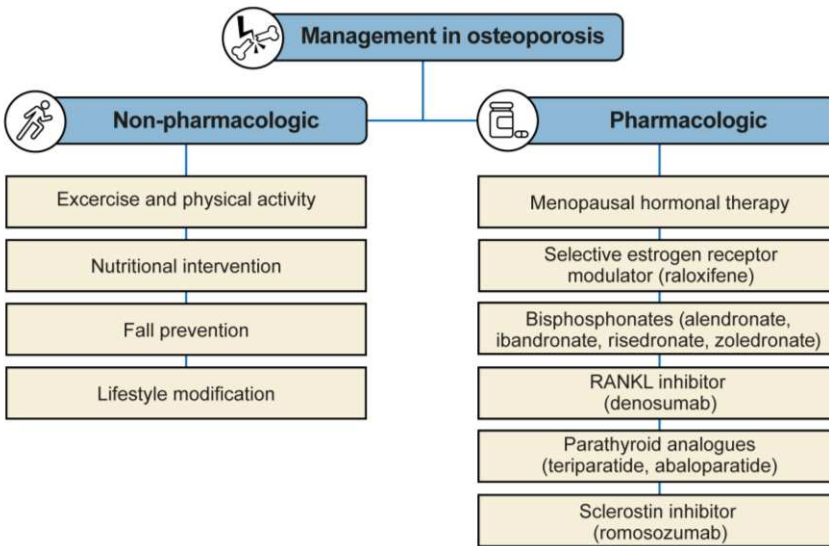
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1 Figures and tables

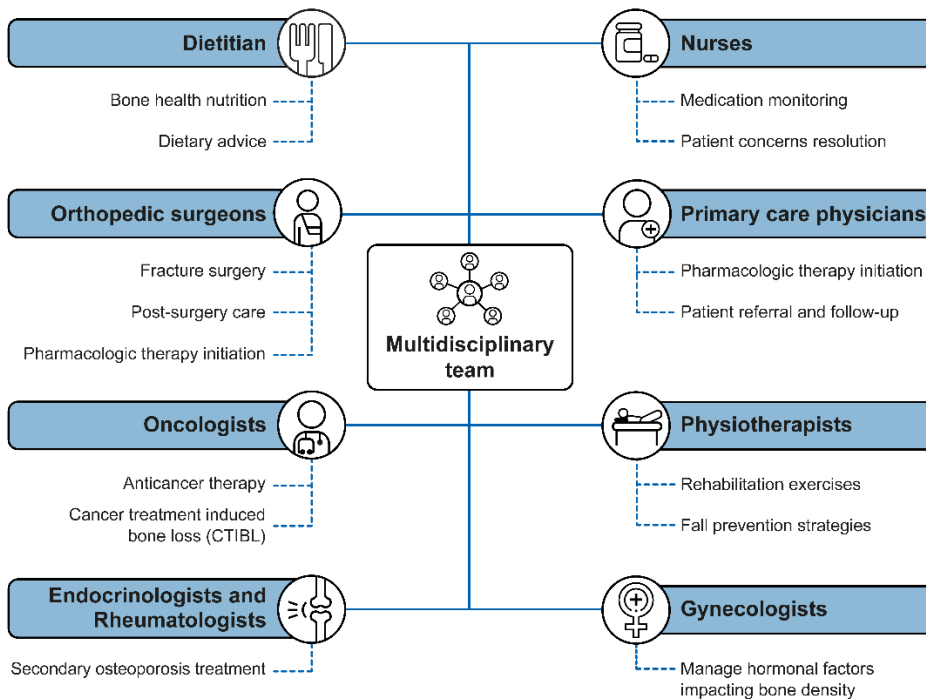
2 **Fig. 1** Management approaches in osteoporosis



3

4 RANKL, receptor activator of nuclear factor-kappa B ligand

5 **Fig. 2** Multidisciplinary management of osteoporosis



6

7

1 **Table 1** Key features of biosimilars [5,6,43–45]

Approval pathway	Both stringent, requiring demonstration that there are no clinically meaningful differences in safety, purity, and potency compared with the reference medicine, and abbreviated, as unlike new medicine development the biosimilar pathway aims to confirm comparability to the reference medicine rather than establish efficacy
Authorization of indications	Approved for one indication of the reference medicine; can be approved for other indications without the need for direct clinical trials, based on the totality of evidence supporting its biosimilarity
Interchangeable	Biosimilars are approved as interchangeable by the EMA and Heads of Medicines Agency; the US FDA currently requires additional switching studies for biosimilars seeking interchangeable status, but it has recently proposed removing this requirement if adequate comparative data are provided

2

3 EMA, European Medicines Agency; FDA, Food and Drug Administration

4

5 Figure legend

6 **Fig. 1** Management approaches in osteoporosis

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10