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Review article

A scoping review on the efficacy, effectiveness, and safety of different pharmacological therapies for the management of patients with glucocorticoid-induced osteoporosis

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Abstract

Introduction: Glucocorticoid-induced osteoporosis (GIOP) is a common secondary osteoporosis resulting from chronic corticosteroid use. It affects bone homeostasis, leading to significant reductions in bone mineral density (BMD) and an increased risk of vertebral and non-vertebral fractures. Due to the increasing number of patients requiring long-term glucocorticoid therapy, a comprehensive understanding of pharmacological interventions available for glucocorticoid-induced osteoporosis is essential.

Objective: To evaluate the efficacy, effectiveness, and safety of different pharmacological therapies used in the management of patients with glucocorticoid-induced osteoporosis through a scoping review of the available literature.

Methods: Following the Joanna Briggs Institute (JBI) methodology, a scoping review was conducted using major databases (PubMed, Embase, Cochrane, and others). Studies including adults with glucocorticoid-induced osteoporosis treated with pharmacological therapies such as bisphosphonates, denosumab, teriparatide, and others were considered. Outcomes focused on changes in bone mineral density, fracture risk reduction, and treatment safety. A total of 40 studies were included (39 on efficacy, 1 on effectiveness, and 12 on safety).

Results: Bisphosphonates (e.g., risedronate, alendronate, and zoledronate) significantly improved lumbar spine bone mineral density (up to +4.8%; with variability across studies, including mean changes around +4.9% ± 4.5% in randomized controlled trials [RCTs])

Highlights

- Bisphosphonates are the first-line treatment for GIOP, reducing fracture risk and improving bone mineral density.
- Teriparatide and denosumab demonstrate strong efficacy in increasing BMD but may face cost and accessibility limitations.
- Adverse events from GIOP therapies are generally mild, with gastrointestinal and flu-like symptoms being most common.
- Real-world effectiveness data are limited, underscoring the need for further long-term outcome studies.

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and reduced vertebral fracture risk (by up to 82.4%). Teriparatide demonstrated superior efficacy in increasing bone mineral density (+7.8% to +11.0%) and reducing fracture incidence, especially in high-risk patients. Denosumab also showed notable improvements in bone mineral density and bone turnover markers. Adverse events were generally mild, with gastrointestinal and flu-like symptoms being the most commonly reported.

Discussion: Bisphosphonates remain the first-line therapy for glucocorticoid-induced osteoporosis due to their efficacy and safety profile. Teriparatide may be preferable for high-risk patients or those with severe bone formation suppression. Denosumab is a valid alternative, particularly for patients who are intolerant to bisphosphonates. This review highlights the importance of individualized therapy based on fracture risk and comorbidities.

Keywords: Osteoporosis, Glucocorticoids, Fractures, Bone, Bisphosphonates, Alendronate, Bone Density.

Revisión de alcance sobre la eficacia, efectividad y seguridad de diferentes terapias farmacológicas para el manejo de pacientes con osteoporosis inducida por glucocorticoides

Resumen

Introducción: la osteoporosis inducida por glucocorticoides (OIG) es una forma común de osteoporosis secundaria resultante del uso crónico de corticosteroides. Afecta la homeostasis ósea, lo que conduce a reducciones significativas en la densidad mineral ósea (DMO) y a un mayor riesgo de fracturas vertebrales y no vertebrales. Debido al aumento del número de pacientes que requieren tratamiento a largo plazo con glucocorticoides es esencial una comprensión integral de las intervenciones farmacológicas para la osteoporosis inducida por glucocorticoides.

Objetivo: evaluar la eficacia, efectividad y seguridad de diferentes terapias farmacológicas utilizadas en el manejo de pacientes con osteoporosis inducida por glucocorticoides a través de una revisión de alcance de la literatura disponible.

Métodos: siguiendo la metodología del Instituto Joanna Briggs (JBI), se realizó una revisión de alcance utilizando las principales bases de datos (PubMed, Embase, Cochrane y otras). Se incluyeron estudios en adultos con osteoporosis inducida por glucocorticoides tratados con terapias farmacológicas como bisfosfonatos, denosumab, teriparatida, entre otros. Los desenlaces se enfocaron en los cambios en la densidad mineral ósea, la reducción del riesgo de fracturas y la seguridad del tratamiento. Se incluyeron un total de 40 estudios (39 sobre eficacia, 1 sobre efectividad y 12 sobre seguridad).

Resultados: los bisfosfonatos (por ejemplo, risedronato, alendronato y zoledronato) mejoraron significativamente la densidad mineral ósea de la columna lumbar (hasta un + 4,8 %; con variabilidad entre estudios, incluyendo cambios medios de aproximadamente +4,9 % ± 4,5 % en ensayos clínicos aleatorizados [ECA]) y redujeron el riesgo de fracturas vertebrales (hasta en un 82,4 %). La teriparatida mostró una eficacia superior tanto en el aumento de la densidad mineral ósea (+7,8 % a +11,0 %) como en la reducción de la incidencia de fracturas, especialmente en pacientes de alto riesgo. El denosumab también mostró mejoras notables en la densidad mineral ósea y en los marcadores de recambio óseo. Los eventos adversos fueron generalmente leves, siendo los síntomas gastrointestinales y el síndrome pseudogripal los más comunes.

Discusión: los bisfosfonatos continúan siendo la terapia de primera línea para la osteoporosis inducida por glucocorticoides debido a su perfil de eficacia y seguridad. La teriparatida puede ser preferible en pacientes de alto riesgo o con supresión severa de la formación

Destacados

- Los bisfosfonatos son el tratamiento de primera línea para la OIG, reduciendo el riesgo de fracturas y mejorando la densidad ósea.
- La teriparatida y el denosumab muestran una alta eficacia en el aumento de la densidad mineral ósea, aunque pueden tener limitaciones de costo y acceso.
- Los eventos adversos de las terapias para la OIG son generalmente leves, con síntomas gastrointestinales y similares a la gripe como los más habituales.
- Los datos sobre la efectividad en la práctica clínica real son limitados, lo que resalta la necesidad de más estudios a largo plazo.

ósea. El denosumab es una alternativa válida, especialmente para pacientes intolerantes a los bisfosfonatos. La revisión destaca la importancia de una terapia individualizada basada en el riesgo de fractura y las comorbilidades.

Palabras clave: osteoporosis, glucocorticoides, fracturas óseas, hueso, bisfosfonatos, alendronato, densidad ósea.

Introduction

Osteoporosis is a highly prevalent disease, particularly in individuals over 50 years old, and represents a significant global healthcare burden. In countries such as the United Kingdom, osteoporosis-related hip fractures have alarmingly high mortality rates, reaching up to 30% within the first year after the injury. Despite advances in treatment and screening, population aging is expected to increase the incidence of these fractures, highlighting the urgency of implementing effective care models and evaluating new therapeutic strategies, particularly for preventable forms such as glucocorticoid-induced osteoporosis. This specific type of osteoporosis results from prolonged glucocorticoid use, which disrupts bone homeostasis, significantly increasing the risk of fractures in patients of all ages, regardless of other risk factors (1-2).

The management of glucocorticoid-induced osteoporosis involves both timely diagnosis and the implementation of effective pharmacological therapies. These include bisphosphonates such as alendronate and zoledronate, alternative therapies such as denosumab, and advanced options such as teriparatide for refractory cases (3). However, while systematic reviews exist for specific treatments, they are limited in scope, addressing only specific research questions and failing to comprehensively cover all aspects of the disease. Given this gap in the literature, a scoping review can map the available evidence, identify knowledge gaps, and provide a broader and more comprehensive perspective on the subject.

In this context, conducting a scoping review that integrates evidence on the effectiveness, safety, and adverse events associated with the available pharmacological therapies for glucocorticoid-induced osteoporosis is crucial. This review aims not only to describe the efficacy of these treatments but also to characterize the available evidence across different patient populations, therapies, and underlying causes of the disease. The findings of this review will provide a solid foundation for improving therapeutic decision-making and promoting the development of future research in this field.

Methodology

This review followed the recommendations provided in the Joanna Briggs Institute (JBI) protocol for scoping reviews (4).

- **Population:** Patients over 18 years old diagnosed with glucocorticoid-induced osteoporosis, with or without fractures, who received various pharmacological therapies for osteoporosis.
- **Concept:** Efficacy (positive outcomes under controlled conditions), effectiveness (positive outcomes in real-world conditions), and safety (adverse event profile) of therapies, including bisphosphonates, monoclonal antibodies and RANK ligand inhibitors, pyridine derivatives, estradiol derivatives and estrogen receptor antagonists, synthetic analogs of parathyroid hormone-related protein, and anti-sclerostin agents.
- **Context:** Patients in hospitalization, emergency, and outpatient settings worldwide, across diverse cultures and genders.

Selection criteria

Studies including subjects with glucocorticoid-induced osteoporosis (GIOP), defined as bone loss caused by chronic glucocorticoid use, with a daily dose of 5 mg or more of prednisone for

at least three months, were selected. Diagnosis was established through bone densitometry, with a T-score ≤ -2.5 compared to a healthy young population (5).

Additionally, study participants must have been treated with bisphosphonates, monoclonal antibodies and RANK ligand inhibitors, pyridine derivatives, estradiol derivatives and estrogen receptor antagonists, synthetic analogs of parathyroid hormone-related protein, and anti-sclerostin agents.

The efficacy of pharmacological therapies—understood as the extent to which a treatment produces the desired effect under controlled study conditions (i.e., clinical trials)—was assessed based on the reduction in fracture risk (vertebral, non-vertebral, and hip fractures), the reduction in fracture incidence at 12 and 24 months, and the increase in bone mineral density (BMD).

On the other hand, effectiveness, which reflects the real-world impact of treatment in routine clinical practice, was evaluated based on the reduction in fracture incidence in a broader, less controlled setting. The safety of treatments was analyzed by considering the incidence of drug-related adverse effects, aiming to determine the tolerability and risks associated with treatment in patients.

A total of 38 studies evaluating efficacy, 1 study evaluating effectiveness, and 12 studies evaluating both efficacy and safety were identified.

Types of evidence sources

Included studies comprised randomized controlled trials (RCTs), non-randomized controlled trials, and systematic reviews that assessed the effectiveness, efficacy, and safety of different pharmacological therapies for the treatment of osteoporosis. Additionally, observational analytical studies, such as prospective and retrospective cohort studies and case-control studies, were considered to evaluate the long-term safety of treatments for patients with glucocorticoid-induced osteoporosis (GIOP).

Search strategy

Searches were conducted in the following electronic databases: Medline, Embase, Clinical Trials, Cochrane, and the Central Register of Controlled Trials (CENTRAL). A complementary search was performed in Google Scholar, OpenGrey, Scopus, and the Web of Science Core Collection.

The search terms used were osteoporosis, drug therapy, drugs, pharmacotherapy, pharmacological treatment, and medication. No restrictions were applied regarding publication date or language.

After the search, all identified citations were collected and screened using Rayyan version 2016 (Clarivate Analytics, PA, USA).

Below is the search strategy for the main databases:

PubMed:

(("Glucocorticoid-Induced Osteoporosis"[MeSH] OR "glucocorticoid-induced osteoporosis" OR "steroid-induced osteoporosis") AND ("Drug Therapy"[MeSH] OR "Pharmacological Treatment" OR "pharmacotherapy" OR "medication") AND ("Efficacy" OR "Effectiveness" OR "Safety"))

Embase:

('glucocorticoid-induced osteoporosis'/exp OR 'glucocorticoid-induced osteoporosis' OR 'steroid-induced osteoporosis') AND ('drug therapy'/exp OR 'pharmacological treatment' OR 'pharmacotherapy' OR 'medication') AND ('efficacy' OR 'effectiveness' OR 'safety')

Lilacs:

((tw:(glucocorticoid-induced osteoporosis)) OR (tw:(steroid-induced osteoporosis))) AND ((tw:(drug therapy)) OR (tw:(pharmacological treatment)) OR (tw:(pharmacotherapy)) OR (tw:(medication))) AND ((tw:(efficacy)) OR (tw:(effectiveness)) OR (tw:(safety))).

Study selection

After retrieving the references, duplicates were removed, and two independent reviewers (JA, GT) screened the titles and abstracts using the Rayyan software. Full-text articles selected for review were analyzed by two independent reviewers (JA, GT) to assess compliance with their eligibility according to the inclusion criteria. Any disagreements between the reviewers were resolved through discussion or with the involvement of an additional reviewer (JA).

Data extraction

Data from eligible studies were recorded in an Excel spreadsheet. The extracted characteristics included publication details, authors, year of

publication, study location, study type, funding source, a general description of the methods, outcome measures, and results.

Once the data from eligible articles were obtained and organized, the results were discussed with the review supervisor. Any disagreements were resolved accordingly by reviewing the objectives of the study and with the assistance of a third reviewer.

Ethical considerations

The authors declare that, because this work involved only a review of existing literature, it did not entail any procedures involving human participants or animals. Therefore, neither institutional ethics committee approval nor informed consent was required for this manuscript. All studies included in this scoping review had already obtained the necessary ethical clearances and informed consent in their original publications, in accordance with applicable guidelines and regulations.

Results

The initial search across various databases and registries identified 4.590 studies. During the screening stage, 1.614 studies were removed as duplicates, leaving 2.976 studies. These were further assessed based on their title and abstract, resulting in the exclusion of 2.719 studies. Thus, 257 studies remained for full-text evaluation. Of these, 217 studies were excluded for the following reasons: 11 due to duplication, 15 for being case series, 11 for being narrative reviews, 83 for addressing primary osteoporosis, and 97 for addressing secondary osteoporosis caused by other conditions. Ultimately, 40 studies were included: 39 assessed efficacy, of which 12 also evaluated safety, and 1 focused on real-world effectiveness. For better clarity, the results of the search and selection process are presented in a PRISMA flow diagram (figure 1).

The data were then classified based on three key criteria: efficacy, effectiveness, and safety of treatments for glucocorticoid-induced osteoporosis (GIOP).

Of the 39 studies that assessed the efficacy of pharmacological therapies for glucocorticoid-induced osteoporosis, most were randomized controlled trials (RCTs) conducted under optimal conditions, controlling for external variables and using comparators such as placebo or standard treatment. Bisphosphonate therapy was found to be highly effective in this context. Reid *et al.* (6) reported that risedronate significantly increased bone mineral density (BMD) and reduced the incidence of vertebral fractures. However, Hoes *et al.* (7) found no significant differences between alendronate and alfacalcidol in fracture reduction, although 24% of patients developed new vertebral fractures.

On the other hand, Eastell *et al.* demonstrated that teriparatide was more effective than alendronate in promoting bone formation in these patients (8), a finding also supported by Payer *et al.* (9), who reported significant increases in BMD with teriparatide.

Similarly, Struys *et al.* (10) and Ringe *et al.* (11) confirmed that etidronate and ibandronate, respectively, increased BMD compared to other treatments. In addition, Devogelaer *et al.* (12) reported that zoledronate led to greater reductions in bone turnover markers compared to risedronate, while Kasayama *et al.* (13) demonstrated that alendronate significantly improved BMD in asthmatic patients compared to alfacalcidol. In a combination therapy approach, Lems *et al.* (14) found that the co-administration of etidronate and sodium fluoride improved bone mineral density (BMD). Similarly, Fuji *et al.* (15) and Kikuchi *et al.* documented that risedronate and the combination of bisphosphonates with vitamin D3, respectively, increased BMD in patients with chronic kidney disease and glomerular diseases (16). Likewise, Lane *et al.* (17) and Farahmand *et al.* (18) reported that parathyroid hormone (PTH 1-34) improved BMD and vertebral strength, respectively, in patients receiving glucocorticoid treatment.

Additionally, Thomas *et al.* (19) observed significant reductions in vertebral and non-vertebral fractures with alendronate and risedronate, a finding supported by Li *et al.* (20), who reported improvements in BMD with ibandronate in women with systemic lupus erythematosus.

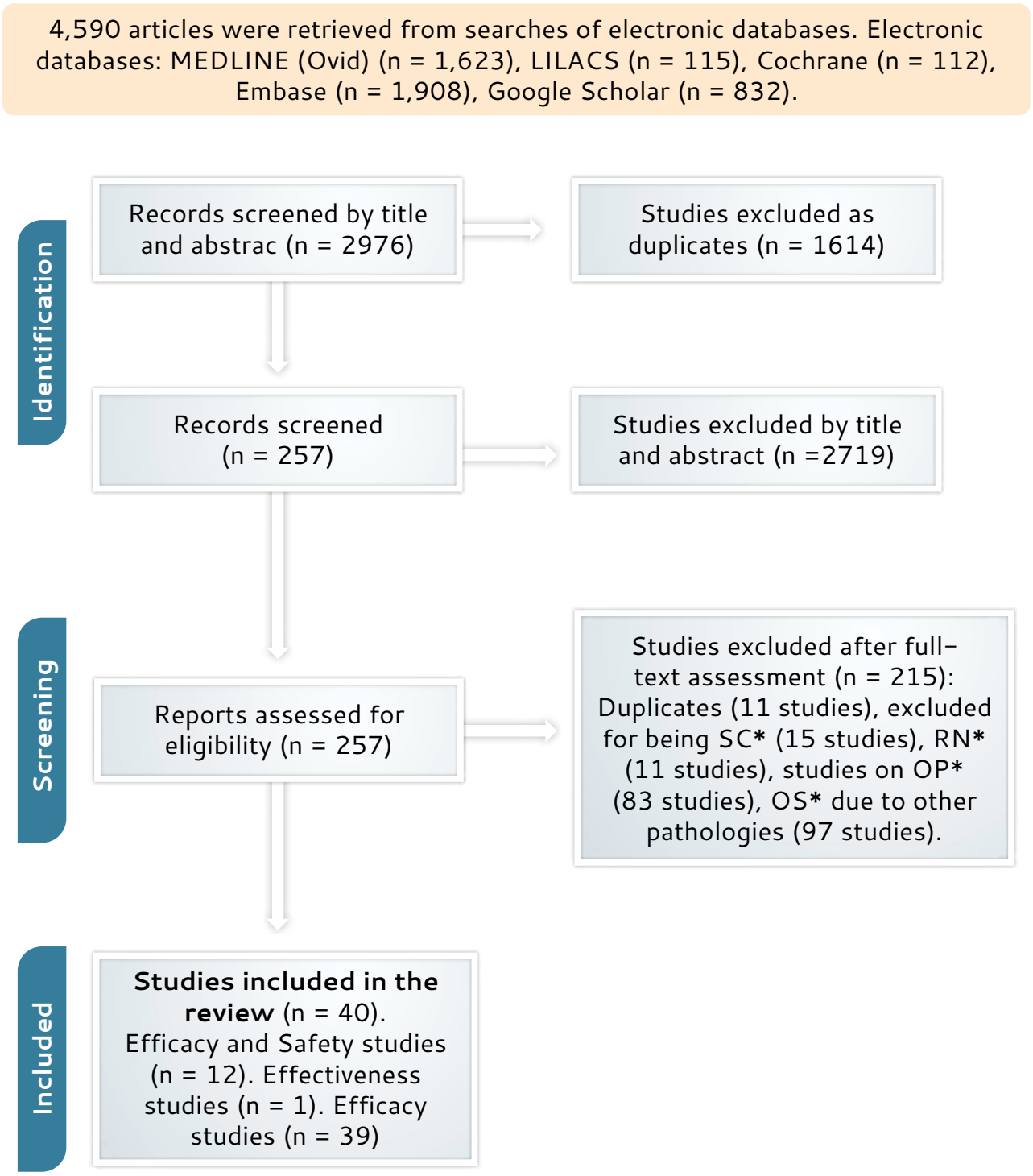

Figure 1. PRISMA flow diagram of selected studies

SC: Case Series; RN: Narrative Reviews; OP: Primary Osteoporosis; OS: Secondary Osteoporosis.

Source: Own elaboration.

Stoch *et al*. (21) and Buxton *et al*. reinforced these findings, demonstrating that alendronate increased BMD and that PTH therapy enhanced bone formation (22). However, Nordborg *et al*. found no significant differences between clodronate and calcium in BMD among patients with giant cell arteritis (23). In contrast, Losada *et al*. demonstrated that teriparatide was more effective than alendronate in increasing BMD in Hispanic patients with glucocorticoid-induced osteoporosis (24).

Switching from bisphosphonates to denosumab or teriparatide was beneficial for improving BMD, according to Ebina *et al*. (25). Meanwhile, Braith *et al*. demonstrated that the combination of alendronate and exercise restored BMD in post-transplant patients (26).

Sambrook *et al*. also indicated that alendronate was superior to calcitriol and vitamin D in preventing bone loss (27). Additionally, Saag *et al*. (2007) and Saag *et al*. (2019) confirmed that teriparatide and denosumab, respectively, were more effective than alendronate and risedronate in increasing BMD and reducing vertebral fractures (28-29).

In 2009, Saag *et al*. found that zoledronic acid was more effective than risedronate in preventing bone loss, while in 2016, they showed that teriparatide improved trabecular bone scores more than alendronate (30-31).

Finally, Roux *et al*., Rehman *et al*., Devogelaer *et al*., and Liu *et al*. concluded that zoledronate, parathyroid hormone, and teriparatide, respectively, were effective in improving BMD and reducing fracture risk in patients with glucocorticoid-induced osteoporosis (GIOP) (32–35). Hirooka *et al*. found that switching to teriparatide significantly increased BMD in the lumbar spine and femoral neck at 12 months (36-37).

On the other hand, Inoue *et al*. demonstrated that multidetector computed tomography (MDCT) enabled more precise detection of bisphosphonate efficacy in glucocorticoid-induced osteoporosis. This method showed significant improvements in bone volume fraction (BV/TV, $p = 0.004$) and trabecular separation (Tb.Sp, $p = 0.015$). In contrast, conventional methods such as DEXA and bone turnover markers failed to identify significant differences between treatments ($p > 0.05$), highlighting the advantage of MDCT in assessing bone microarchitecture (38).

Similarly, Soen *et al*. compared the efficacy of minodronate combined with alfacalcidol versus alfacalcidol alone for the treatment of glucocorticoid-induced osteoporosis. In this randomized study, after 24 months, patients who received the combination therapy showed a significant increase in lumbar spine BMD (4.0% vs. -0.2% in the alfacalcidol-only group, $p = 0.0003$) and total hip BMD (3.2% vs. -3.0%, $p < 0.0001$). Additionally, a significant reduction in bone turnover markers was observed in the combination group, with a 57% decrease in TRACP-5b at 3 months, which remained stable up to 24 months (39).

Similarly, Iseri *et al*. (40) conducted a randomized trial showing that, after 12 months, denosumab treatment significantly increased lumbar spine BMD by 5.3%, compared to a 2.0% increase in the alendronate group ($p < 0.05$). Moreover, denosumab reduced bone turnover markers more effectively than alendronate. While both treatments were effective in reducing these markers, denosumab resulted in greater suppression (40).

Similarly, Jinnouchi *et al*. evaluated a one-year of treatment regimen with etidronate and vitamin D3 in 25 patients. The results showed that the combination group had a significant improvement in bone mineral levels (YAM, $p < 0.05$) and a reduction in bone resorption compared to the group treated with vitamin D3 alone. Additionally, the combination group had a lower incidence of new vertebral compression fractures, suggesting that etidronate is effective in preventing bone loss and fractures in these patients (41).

Kanis *et al*. evaluated clinical studies and cost analyses for the treatment of glucocorticoid-induced osteoporosis, focusing primarily on the prevention of vertebral and non-vertebral fractures. This analysis highlighted that both risedronate and calcidiol showed significant efficacy in reducing vertebral fractures. Additionally, risedronate was assessed in terms of cost-effectiveness in patients with risk factors, such as advanced age and a history of fractures. The study also proposed a treatment algorithm based on bone mineral density (BMD) and individual risk factors (42).

Finally, Langdahl *et al*. analyzed the efficacy of teriparatide versus alendronate in treating GIOP in patients of different genders and menopausal statuses. After 18 months, the results showed that teriparatide significantly increased lumbar spine BMD compared to alendronate in postmenopausal women (7.8% vs. 3.7%, p < 0.001), premenopausal women (7.0% vs. 0.7%, p < 0.001), and men (7.3% vs. 3.7%, p = 0.03). Additionally, a lower incidence of vertebral fractures was observed in the teriparatide group (1 case) compared to the alendronate group (10 cases), further emphasizing the superior efficacy of teriparatide in increasing BMD and reducing fractures in patients with glucocorticoid-induced osteoporosis (43).

Table 1 summarizes the articles related to the efficacy of therapies for glucocorticoid-induced osteoporosis.

Table 1. Characteristics of the included studies on the efficacy of treatments for glucocorticoid-induced osteoporosis

Author, year, and study design	Population and age	Intervention (name), n, and dose	Intervention outcome	Comparator (name), n, and dose	Main outcome
Reid *et al*. (2001). Randomized clinical trial (6)	Men, outpatient setting, aged 18 to 85 years.	RIS* n = 124 Tab 2.5 mg (n = 61), Tab 5 mg (n = 63).	Increase in BMD* by 4.8% in the lumbar spine with 5 mg of RIS*.	Placebo n = 60	RR*: Vertebral fractures: 82.4% lower risk with RIS* (95% CI: 36.6% – 95.1%, p = 0.008). MD* Increase in BMD* with RIS* 5 mg: Lumbar spine: +4.8% Femoral neck: +2.1% Trochanteric region: +2.6%. BMD* loss in the placebo group: Lumbar spine: −3.4% Femoral neck: −3.3% Trochanteric region: −3.4%
Hoes *et al*. (2010). Cohort study (7)	Patients with an inflammatory rheumatic disease. Outpatient setting.	ALN* n = 116 Tab 10 mg orally daily or ALF* cap 1 µg orally daily. Patients were not categorized by intervention type in the summary.	24% of patients developed at least one new vertebral fracture.	N/A	OR*: Vertebral fractures: 1.00016 (95% CI: 1.00003 – 1.00029; p < 0.05) per mg of cumulative GC* dose. Age: 1.14 (95% CI*: 1.05 – 1.23; p < 0.05) per year of age increase. MD*: Lumbar spine: +0.4% ± 5.9% Femoral neck: −0.18% ± 5.4% Total hip: +0.07% ± 4.8% RR*: 24% of patients developed at least one new vertebral fracture.

Eastell *et al.* (2010). Randomized clinical trial (8)	Men and women ≥ 21 years. Outpatient setting.	TPTD*, n = 97 Amp 20 µg/day subcutaneous administration.	Increase of 92% in OC* and 108% in PINP*	ALN* n = 100 Tab 10 mg/day orally.	OR*: Vertebral fractures with TPTD* vs. ALN*: 0.22. MD*: Increase in BMD* at 12 months: Lumbar spine: TPTD*: Up to 11%. ALN*: Up to 3% RR: TPTD*: 0.22 for vertebral fractures.
Burshell *et al.* (2010). Randomized clinical trial (8)	Men and women aged 22 to 89 years. Outpatient setting.	TPTD* n = 80 Amp 20 µg/day subcutaneous administration.	Significant increase in lumbar spine BMD* (mean ± SE) of +7.2% and femoral neck BMD* of +3.8% at 18 months.	ALN* n = 77 Tab 10 mg/day orally.	MD* TPTD*: Lumbar spine: Increase in BMD*: $p < 0.001$. Femoral neck: Increase in BMD*: $p < 0.01$
Payer *et al.* (2018). Non-randomized clinical trial (9)	Men, mean age: 57.3 ± 12.1 years. Women, age: 59.7 ± 14.8 years. Outpatient setting.	TPTD*, n = 129 Amp 20 µg/day subcutaneous administration Ca* supplements: 500-1000 mg/day orally V.D3*: 400-800 IU/day orally.	Increase in BMD* in lumbar spine (n = 122): +8.3% at 12 months ($p < 0.001$) and +9.28% at 18 months ($p < 0.001$). Increase in BMD* in total hip (n = 116): +3.85% at 18 months ($p < 0.001$). Increase in BMD* in femoral neck: +3.26% ($p < 0.001$).	N/A	MD*: Increases in BMD* after 18 months of treatment with TPTD: Lumbar spine: +9.28% ($p < 0.001$). Total hip: +3.85% ($p < 0.001$). Femoral neck: +3.26% ($p < 0.001$)
Kasayama *et al.* (2005). Randomized clinical trial (13)	Japanese postmeno-pausal women diagnosed with bronchial asthma, with no recent use of systemic corticosteroids. Outpatient setting.	ALN* n = 18 Tab 5 mg/day orally.	Increase in BMD*: Lumbar spine: +4.9% ± 4.5%. Total hip: +2.4% ± 2.2%. Ward's triangle: +3.6% ± 5.2% at 12 months.	ALF* n = 10 Tab 1 µg/day orally.	MD*: Increases in BMD* after 12 months of treatment: Lumbar spine: ALN*: +4.9% ($p = 0.0005$). ALF*: +1.7% (not significant, $p = 0.255$). Total hip: ALEN*: +2.4% ($p = 0.0005$). ALF*: +0.1% (not significant, $p = 0.949$). Ward's triangle: ALN*: +3.6% ($p = 0.02$). ALF*: +2.0% (not significant, $p = 0.484$).

Struys *et al.* (1995). Randomized clinical trial (10)	Men and women. Outpatient setting.	ETD*n = 19 Tab 400 mg/ day for 14 days, followed by Ca* 500 mg/day for 76 days (4 cycles).	Increase of 5.7% in lumbar spine (L1-L4) BMD*. Increase of 6.8% in proximal femur (total hip) BMD*.	Ca* supplemen-tation n = 20	Significant BMD* loss: 3.4% in the lumbar spine and 4.1% in the proximal femur.
Ringe *et al.* (2003). Randomized clinical trial (11)	Men and women, mean age: 64 years. Outpatient setting.	IBN* n = 58 Ampoule 2 mg, intravenous injections every 3 months.	Increase of 13.3% in lumbar spine BMD*. 62.3% reduction in the risk of new vertebral fractures (8.6% incidence). Increase of 5.2% in femoral neck BMD*. Reduction in lumbar pain in 86.2% of patients.	ALF* n = 57. Tab 1 mcg orally daily.	MD*: Increase in BMD* after 12 months. Lumbar spine: ETD*: +5.7% ($p < 0.02$ vs. baseline, $p < 0.001$ vs. Ca* group). Ca*: -3.4% ($p < 0.02$ vs. baseline). Proximal femur (total hip): ETD*: +6.8% ($p < 0.02$ vs. baseline, $p < 0.001$ vs. Ca* group). Ca*: -4.1% ($p < 0.02$ vs. baseline).
Devogelaer *et al.* (2013). Randomized clinical trial (12)	Men and women aged 18 to 85 years.	ZOL* 5 mg IV annually. Treatment subpopulation: n = 272.	Reduction in b-CTx*: 62%, 59%, 65%. NTx* reduction: 20-33% P1NP* reduction: 9-33% BSAP* reduction: 4-14%.	Risedronate 5 mg orally daily 417 patients received RIS*	MD*: Reduction in bone turnover markers after 12 months: b-CTx*: ZOL*: 40-62% ($p < 0.05$). RIS*: 30-46%. NTx*: ZOL*: Reduction of 20-30%. Bone formation markers: P1NP*: ZOL*: 22% ($p < 0.05$). BSAP*: ZOL*: 14-20% ($p < 0.05$).
Kasayama *et al.* (2005). Randomized clinical trial (13)	Japanese postmenopausal women diagnosed with bronchial asthma, with no recent use of systemic corticosteroids, among others.	Alendronate: n = 16, 5 mg/ day.	Oral ALN* 5 mg/d for 12 months significantly increased BMD*: lumbar spine +4.9% ($p = .0005$), total hip +2.4% ($p = .0005$), Ward's triangle +3.6% ($p = .02$).	ALF* n = 9, 1 µg/day.	MD*: Increase in BMD* with ALN* 5 mg: Lumbar spine: +4.9%, Total hip: +2.4%, Ward's triangle: +3.6%. Change with ALF* 1 µg: Lumbar spine: +1.7%, Total hip: +0.1%, Ward's triangle: +2.0%. Markers: Greater reduction in bone turnover markers (NTx, OC*, AF*) with Alendronate.

Lems *et al.* (1997). Randomized clinical trial (14)	Patients on corticosteroids ≥7.5 mg/day.	NaF* + cyclical ETD*, n = 23, NaF 25 mg BID + ETD* 200 mg BID* for 2 weeks every 3 months.	Lumbar spine BMD* ↑ +9.3% (95% CI*: +2.3% to +16.2%, p < 0.01); Hip BMD*: no significant change (−2.5%, NS).	Placebo + cyclical ETD*, n = 24, placebo BID* + ETD* 200 mg BID* for 2 weeks every 3 months.	MD*: Lumbar spine BMD* ↑ +9.3% (95% CI: +2.3% to +16.2%, p < 0.01) vs. +0.3% (95% CI*: −2.2% to +2.8%) with placebo. Δ between groups: +8.9% (95% CI: +1.9% to +16.0%, p < 0.01). Hip BMD* ↓ −2.5% (NS*) vs. −4.0% (p < 0.01), Δ = +1.5% (NS*).
Fuji *et al.* (2007). Randomized clinical trial (15)	CKD* patients with GIOP*, age: 42.5 ± 16.6	RIS*, n = 50 (with aVD*), 2.5 mg/d PO* RIS*, n = 28 (without aVD*), 2.5 mg/d PO*	Lumbar spine BMD* ↑ 2.8% (with aVD*) and ↑ 2.1% (without aVD*) at 12 mo S-NTX* ↓ ~20%, ALP* ↓ ~11% at 6 mo*	aVD* only, n = 37, mean dose 0.36 mg/d	Lumbar spine BMD* ↓ 1.2% (NS*) S-NTX* unchanged, ALP* ↑ 26.9% RIS improved BMD* vs aVD* (p < 0.05)
Kikuchi *et al.* (2007). Randomized clinical trial (16)	Patients with glomerular diseases; mean age 42 ± 16 years.	Group R: Risedronate, n=12, 2.5 mg/ day Group R+A: Risedronate + Alfacalcidol, n=11, 2.5 + 0.5 mg/day.	R: No significant change in BMD* R+A: BMD* ↑ +2.0% overall, +2.1% in patients receiving steroid pulses.	Group A: Alfacalcidol only, n=15, 0.5 mg/day.	Lumbar BMD changes: R: stable R+A: Significant increase A: Significant decrease (−5.6%) Urinary NTx*: decreased in R and R+A, unchanged in A Bone formation markers (OC*, ALP*): decreased in all groups Baseline urinary NTx* was higher in patients with BMD* loss.
Lane *et al.* (2000). Randomized, controlled, parallel-group trial (17)	Postmenopausal women; age 50–82 yrs, with GIOP* on ≥1 year of HRT and prednisone 5–20 mg/day.	PTH (1–34)*: n=28, 400 IU/ day SC*	↑ Spine BMD*: +35% (QCT*), +11% (DXA*) at 12 mo (p < 0.001); sustained ↑ at 24 mo. ↑ bone markers (BSAP*, OC*); delayed ↑ in DPD.	Control group: n=21; no PTH*; continued HRT*, glucocorticoids, calcium (1500 mg/day) + Vitamin D (800 IU/day)	Early ↑ in bone formation markers (BAP*, OC*) predicted spine BMD* gains. Marker response (1–6 mo) correlated with 12–24 mo BMD* ↑. ROC* AUC* >0.79 for QCT* prediction.

Farahmand *et al.* (2013). Controlled clinical trial (18)	Ambulatory men with GIO*; mean age 56.3 yrs (range 25–82).	Teriparatide, n = 45, 20 µg/ day SC*	↑ P1INP* and CTx*; ↑ vertebral strength in all loading modes; strong positive correlation between ↑ P1INP* and vertebral strength at 18 months.	Risedronate, n=47, 35 mg/ week orally.	TPTD* ↑ vertebral strength vs. RIS* at 18 mo in all FEA* modes (e.g., axial compression: 7.08 ± 3.48 vs. 5.95 ± 2.2 kN, p = 0.015); PINP* ↑ significantly with TPTD* (p < 0.001); early PINP* changes correlated with strength gains (e.g., r = 0.560 at 6 mo), supporting PINP* as a surrogate marker of bone strength in GIOP*.
Thomas *et al.* (2013). Observational cohort study using administrative claims data (19)	Women ≥65 yrs on glucocorticoids (GC).	Alendronate, n = 6.359, 70 mg/week Risedronate, n=4,648, 35 mg/week.	ALN: ↓ non-vertebral fracture rate by 33% (from 5.22 to 3.51/100 PY), ↓ vertebral fracture rate by 59% (p < 0.05) RIS: ↓ non-vertebral fracture by 28% (from 5.51 to 3.95/100 PY), ↓ vertebral fracture by 54% (p < 0.05).	N/A*	Both ALN and RIS significantly reduced clinical vertebral and non-vertebral fracture incidence over 12 mo vs. baseline 3-mo rate in women with GIO. Study not designed for head-to-head comparison.
Li *et al.* (2010). RCT, double-blind, placebo-controlled (20)	Chinese women with SLE* on long-term glucocorticoids; mean age 44 ± 8.7 yrs.	Ibandronate, n = 20, 150 mg/ month + daily Alfacalcidol 1 µg + calcium 500 mg/day.	↑ Cortical bone density (Dcomp) (p = 0.023); ↑ aBMD* lumbar spine (+4.9%, p < 0.0001) and hip (+1.0%, p < 0.005); stable microarchitecture.	Placebo, n=20, monthly placebo + daily alfacalcidol 1 µg + calcium 500 mg/day.	IBAN* ↑ cortical Dcomp and preserved microarchitecture (HR-pQCT*); ↑ aBMD* LS vs placebo (4.9% vs 2.6%, p = 0.024); ↓ Tb.Sp* only in placebo (p = 0.04).
Stoch *et al.* (2009). RCT*, double-blind, placebo-controlled, multicenter. (21)	Patients (ALN*: n = 114, placebo: n = 59); mean age ˜52–55 yrs; men and women on ≥7.5 mg/d prednisone for ≥12 months.	Alendronate (ALN), n = 114, 70 mg/ week + calcium 1000 mg/day + vitamin D 400 IU/day.	↑ BMD* lumbar spine: +2.45% (p ≤ 0.001); trochanter:+1.27% (p = 0.007); total hip: +0.75% (p = 0.008); ↓ NTX/ Cr*: −32.2% (p ≤ 0.001).	Placebo, n = 59, + same calcium and vitamin D regimen.	ALN ↑ BMD vs. placebo at 12 mo in LS (+2.92%, p ≤ 0.001), trochanter (+1.66%, p = 0.007), and total hip (+1.19%, p = 0.008); ↓ BSAP (−14.5%, p ≤ 0.001); ALN well tolerated, no sig. difference in AE vs placebo.

Buxton *et al.* (2004). RCT, parallel-group, open-label (22)	Postmenopausal women with GIOP*; age 50–82 yrs.	PTH*(1–34), n = 28; 400 U/day (˜40 µg), SC for 12 months + HRT* + calcium (1500 mg) + vitamin D (800 IU).	↑ sRANKL* (+250% at 3 mo, p < 0.05), ↑ IL-6 (+130% at 3 mo, p < 0.05), ↑ IL-6sR (peak at 1 mo*, p < 0.05), ↓ OPG (–45% at 12 mo); ↑ OC & BSAP* > 100%	HRT alone, n = 23; calcium + vitamin D.	PTH (1–34)* rapidly ↑ bone formation markers (OC*, BSAP*) and osteoblast-derived cytokines (sRANKL*, IL-6*, IL-6sR*), preceding DPD* ↑; supports uncoupling of remodeling in favor of formation during early GIOP* treatment.
Nordborg *et al.* (1997). RCT*, double-blind, placebo-controlled (23)	Patients with GCA on GC*; 21 women / 6 men; mean age 70.2 yrs.	Clodronate, n = 14; 800 mg PO* daily, cyclically every second month (months 1,3,5,7,9,11) + calcium 500–750 mg/day.	No significant effect on BMD or BMC at any time point; ↓ OC at 12 mo vs. control (5.81 ± 2.21 vs. 6.69 ± 2.60 ng/mL, p < 0.05).	Placebo, n = 13; same calcium regimen.	Cyclic oral clodronate did not prevent GC-induced bone loss better than calcium alone; BMD and BMC recovered similarly in both groups.
Losada *et al.* (2009). RCT, double-blind, double-dummy, active comparator-controlled (24)	Patients: Mean age ˜58 yrs; men and women ≥21 yrs with GIO on ≥5 mg/d prednisone for ≥3 months.	TPTD* n = 214; 20 µg/day SC* + calcium 1000 mg/d + vitamin D 800 IU/d.	↑ LS* BMD* +9.8% ±1.7 vs ALN* +4.2% ±1.4 (p < 0.001); ↑ TH* BMD* +5.9% vs +1.3% (p < 0.001); ↑ FN* BMD* +4.3% vs +2.0% (p = 0.228).	ALN*, n = 214; 10 mg/day PO + calcium 1000 mg/d + vitamin D 800 IU/d.	TPTD* showed significantly greater ↑ in LS* and TH* BMD* vs ALN* at 18 mo in both Hispanic and non-Hispanic cohorts; fracture incidence and AEs were similar.
Braith *et al.* (2003). RCT*, prospective, 3-arm, controlled (26)	Heart transplant recipients; all on GC*; mean age: 54–56 yrs.	ALN*+TRN*: n = 8; Alendronate 10 mg/day + supervised resistance training for 6 mo*, starting 2 mo* post-transplant.	BMD* restored to near-baseline at 6 mo*: total body –0.9%, femoral neck –2.1%, lumbar spine –3.4%; significant ↑ vs ALN* or control.	ALN*: n = 8; Alendronate 10 mg/day only. Control: n = 9; no intervention.	ALN*+TRN* more effective than ALN alone in reversing GC-induced BMD* loss in HTR*; combined therapy restored BMD* nearly to baseline at all skeletal sites.
Sambrook *et al.* (2012). RCT*, double-blind, double-dummy, active-controlled (27)	Men (mean age 56.4 yrs) receiving glucocorticoids.	ZOL*, n = 131; 5 mg IV once + daily calcium (1000 mg) + vitamin D (400–1200 IU).	At 12 mo*, ↑ LS* BMD*: +2.46% (prevention), +4.69% (treatment); ↑ TH* BMD*: +1.10% and +1.82%; ↓ β-CTx* & P1NP* > RIS* at all timepoints (p < 0.05–0.001).	RIS*, n = 134; 5 mg PO* daily + same supplements.	ZOL* produced greater ↑ in LS* and TH* BMD* vs. RIS* in both prevention and treatment arms (e.g., LS: +4.69% vs. +3.27%, p = 0.0232); greater ↓ in bone turnover markers.

Saag *et al.* (2007). RCT, double-blind, double-dummy, active-controlled (28)	Adults (345 women, 83 men), aged 22–89 yrs, with GIOP (on ≥5 mg/d prednisone ≥3 mo).	TPTD*, n = 214; 20 µg/day SC* + calcium 1000 mg/day + vitamin D 800 IU/day.	↑ LS* BMD* +7.2% ±0.7 vs ALN* +3.4% ±0.7 ($p < 0.001$); ↑ TH* BMD* +3.8% ±0.6 vs ALN* +2.4% ±0.6 ($p = 0.005$); ↑ bone formation markers, ↓ new vertebral fx (0.6%).	ALN*, n=214; 10 mg/day PO* + same calcium and vitamin D regimen.	TPTD* significantly ↑ LS* and TH* BMD* vs ALN* and ↓ new vertebral fractures (0.6% vs 6.1%, $p = 0.004$); similar nonvertebral fx rate (5.6% vs 3.7%, $p = 0.36$).
Saag *et al.* (2019). RCT, double-blind, double-dummy, active-controlled (29)	Patients with GIO; age ~61–67 yrs.	DMAb*, n=398; 60 mg SC* every 6 mo + daily oral placebo + calcium ≥1000 mg + vitamin D ≥800 IU.	At 12 mo*, ↑ LS BMD*: +4.4% (GC*-continuing), +3.8% (GC*-initiating); TH*: +1.5%; FN*: +1.0% and +1.1%; ↓ CTX* & P1NP* > RIS* ($p < 0.0001$–0.046).	RIS*, n = 397; 5 mg/day PO + SC placebo every 6 mo + same supplements.	DMAb* was non-inferior and superior to RIS* in ↑ LS*, TH*, and FN BMD* at 12 mo (e.g., LS* diff. +2.2% [95% CI* 1.4–3.0]); similar fracture and AE* rates in both arms.
Saag *et al.* (2009). RCT, double-blind, double-dummy, active-controlled (30)	Adults aged 22–89 yrs, with GIOP*; all on ≥5 mg/d prednisone for ≥3 mo*	TPTD*, n = 214; 20 µg/day SC + calcium 1000 mg/day + vitamin D 800 IU/day.	At 36 mo*: ↑ LS BMD* +11.0%, ↑ TH* BMD* +5.2%, ↑ FN* BMD* +6.3%; ↑ bone formation markers (P1INP*, OC*, ALP*) throughout; ↓ new vertebral fx (1.7% vs 7.7%, $p = 0.007$).	ALN*, n=214; 10 mg/day PO + same supplements.	TPTD* led to significantly greater ↑ in BMD* (LS*, TH*, FN*) and fewer vertebral fx vs ALN* over 36 mo*; nonvertebral fx rates similar (7.5% vs 7.0%, $p = 0.843$); TPTD* ↑ serum calcium more frequently.
Saag *et al.* (2016). Subanalysis of RCT*, double-blind, double-dummy, active-controlled (31)	Patients with GIOP*; mean age 58 yrs; median prednisone dose 7.5 mg/day; ~81% female.	TPTD*, n = 56; 20 µg/day SC* + calcium 1000 mg/day + vitamin D 800 IU/day.	↑ LS* BMD* +10.3% and ↑ TBS* +3.7% at 36 mo* ($p < 0.05$); ↑ TBS* from 18 mo* onward ($p < 0.05$ vs baseline and ALN*); weak correlation between BMD* and TBS* changes.	ALN*, n = 53; 10 mg/day PO + same supplements.	TPTD* ↑ both BMD* and TBS*, while ALN* ↑ only BMD*; TBS* was more sensitive to anabolic treatment effects and may better reflect microarchitectural improvements in GIOP*.
Roux *et al.* (2012). Post hoc analysis of RCT*, double-blind, double-dummy, active-controlled (32)	Patients with GIO*; aged 18–85 yrs; on ≥7.5 mg/day prednisone; stratified in treatment.	ZOL*, n = 416; 5 mg IV single infusion + daily PO* placebo + calcium (1000 mg) + vitamin D (400–1200 IU).	At 12 mo*, ZOL* ↑ LS* BMD* significantly vs RIS* in most subgroups (age 35–74, both sexes, postmenopausal women, Vit D >20 ng/mL, CrCl ≥60 mL/min, PPI* use ; $p < 0.05$).	RIS*, n = 417; 5 mg/day PO* + IV placebo + same supplements.	ZOL* was more effective than RIS* in ↑ LS* BMD* across multiple GIO* subgroups (gender, age, Vit D, steroid dose/duration, renal fxn); effect maintained regardless of baseline BMD*.

Devogelaer *et al.* (2010). Post-hoc analysis of RCT*, double-blind, double-dummy, active-controlled (34)	Adults with GIO*; mean age ~56 yrs; baseline GC* categorized as low (≤5 mg/d), medium (>5–<15 mg/d), or high (≥15 mg/d).	TPTD*, n = 195; 20 µg/day SC + calcium 1000 mg/day + vitamin D 800 IU/day.	LS* BMD* ↑: +8.1% (low), +6.6% (medium), +4.6% (high GC* dose); greater ↑ than ALN* at all dose categories; greatest difference in low GC* group (4.5%, p < 0.001).	ALN*, n = 192; 10 mg/day PO* + same supplements.	TPTD* led to significantly greater LS* BMD* gains than ALN overall (+3.6%, p < 0.001), especially in low and medium GC* dose groups; effect diminished at high GC* doses.
Liu *et al.* (2020). NMA* of 51 RCTs* (35)	Patients with GIOP* from 51 RCTs*; age range varies across trials.	Multiple drugs studied: teriparatide, denosumab, raloxifene, ibandronate, pamidronate, etc.; doses per standard RCT protocols (varies by trial).	TPTD* (SUCRA* 95.9%) best at ↓ vertebral fractures (RR* 0.06, 95% CI*: 0.01–0.27); RAL* ↑ LS* BMD* (SMD* 12.56); DEN* ↑ TH BMD (SMD* 12.63).	Placebo and active comparators depending on trial (ALN*, RIS*, CT*, Ca*, VD3*, etc.); variable n/doses across included studies.	TPTD* and IBA* most effective in reducing vertebral and non-vertebral fractures, respectively; RAL* best for LS* BMD* gain, DEN* for TH* BMD*.
Rehman *et al.* (2003). RCT*, prospective, randomized, controlled, open-label (33)	Postmenopausal women with GIO* on chronic HRT* and GC*; mean age: 62 yrs.	hPTH (1–34)*, n = 28; 40 µg/day SC for 12 months + HRT* + calcium 1500 mg + vitamin D 800 IU.	↑ VCSA* +4.8% at 12 mo (p < 0.001), maintained at +2.6% at 24 mo (p < 0.05); ↑ BMD* by QCT* +34.9% at 12 mo, +44.1% at 24 mo*; ↑ vertebral strength +200%	HRT* alone, n = 23; continued estrogen + same calcium/vitamin D regimen.	hPTH (1–34)* significantly ↑ vertebral size and compressive strength vs. HRT* alone; effect sustained 1 year post-treatment, likely due to periosteal apposition.
Inoue *et al.* (2013). RCT, open-label, parallel-group, prospective (38)	Japanese patients with IgA nephropathy on high-dose GC; 10 men; mean age 28.6 yrs; normal renal function.	RIS*, n = 4; 2.5 mg/day PO* (some changed to ALN* 35 mg/week).	MDCT* detected ↑ BV/TV* (+1.5%, p = 0.004), ↓ Tb.Sp* (–13.1%, p = 0.015), ↓ SMI* (–0.13, p = 0.009), ↑ fracture load (+6.5%, p = 0.034); no sig. changes in BMD* or BTMs*.	Calcitriol, n = 5, 0.5 µg/day; Menatetrenone, n = 4, 45 mg/day.	Only MDCT* detected microarchitectural preservation with RIS*; MDCT* superior in assessing short-term bisphosphonate effect in early GIO*.
Soen *et al.* (2020). RCT, multicenter, open-label, parallel-group, comparative study (39)	Patients with GIO*; mean age ~64 yrs (range 34–85); all on ≥5 mg/d prednisone for ≥3 months.	MIN-M* + ALF*, n = 75; MIN-M* 50 mg PO every 4 weeks + ALF* 1 µg/day.	At 24 mo: ↑ LS BMD* +4.0% (p = 0.0003), ↑ TH* BMD* +3.2% (p < 0.0001); ↓ TRACP-5b* (–57%) and P1NP* (–42%) at 3 mo*; effects sustained at 24 mo*	ALF*, n = 77; 1 µg/day.	MIN-M*+ALF* superior to ALF* alone in ↑ LS* and TH* BMD* and ↓ bone turnover markers; vertebral fx incidence not significantly different (HR* 3.3; 95% CI 0.7–16.1, p = 0.089).

Hirooka *et al.* (2020). Prospective, open-label, non-randomized clinical trial (36)	Patients with GIO* and prior bisphosphonate use; mean age: 66.7 (DEN*) vs. 61.1 yrs (TPTD*); all on ≥5 mg/d prednisone; various connective tissue diseases.	TPTD*, n = 21; 20 µg/day SC*	↑ LS* BMD* +7.9% ($p < 0.001$), ↑ FN* BMD* +6.6% ($p < 0.05$), ↑ TH* BMD* +3.3% (NS*); ↑ TRACP-5b* and P1NP* throughout.	DEN*, n = 20; 60 mg SC every 6 mo*	TPTD* showed greater early and sustained ↑ in LS* and FN* BMD* than DEN*; both ↑ LS* BMD* at 24 mo, but only TPTD* ↑ FN* BMD*; DEN* ↓ BTMs*, TPTD* ↑ BTMs*; 2 fx in DEN* group.
Hirooka *et al.* (2021). Prospective, open-label, non-randomized clinical trial (37)	Patients with GIO* and prior bisphosphonate use; mean age ˜63 yrs; connective tissue diseases; all on glucocorticoids (mean PSL ˜3 mg/day).	Teriparatide → Denosumab (Switch group), n = 18; TPTD* 20 µg/day SC* for 24 mo*, then switched to DEN* 60 mg SC every 6 mo*	↑ LS* BMD* +14.2% ($p < 0.001$), ↑ FN* BMD* +11.2% ($p < 0.05$), ↑ TH* BMD* +7.2% ($p < 0.01$); ↑ BTMs* (TRACP-5b*, P1NP*) with TPTD*, then ↓ with DEN*	Continuous denosumab, n = 16; DEN* 60 mg SC* every 6 mo* for 48 mo*	TPTD*→DEN* produced greater ↑ in FN* BMD* vs continuous DEN* at 48 mo ($p < 0.05$); both ↑ LS* and TH* BMD*; suggests benefit of anabolic-to-antiresorptive sequence in GIO*
Iseri *et al.* (2018). RCT*, single-center, open-label, randomized controlled trial (40)	Patients with GIO* and glomerular disease; median age 66 yrs; all on PSL*; bisphosphonate-naïve.	DMAb*, n = 14; 60 mg SC every 6 months + daily calcitriol 0.25 µg.	↑ LS* BMD* +5.3% at 12 mo ($p < 0.01$); ↓ TRACP-5b* −57.7%, BAP* −30.9%, t-PINP* −57.4% (all $p < 0.01$); no sig. ↑ in FN* or UD* BMD*	ALN*, n = 14; 35 mg PO weekly + daily calcitriol 0.25 µg.	DMAb* produced significantly greater ↑ in LS* BMD* vs ALN* at 12 mo* ($p < 0.05$); stronger suppression of BTMs*; no fx* difference; 1 FN* fx in DMAb* group.
Jinnouchi *et al.* (2000). RCT, single-center, open-label, comparative trial (41)	Patients (Group A: n = 9; Group B: n = 16) with GIO* and diffuse connective tissue disease; age ≥20 yrs; all on ≥5 mg/d prednisone.	Group B: Etidronate 200 mg/day PO* ×14 days every 3 months + V.D3 1 µg/day.	↓ DPD* (−18.1 to −20.2%, $p < 0.05$), ↑ YAM* +5.17% and +5.54% at 24 and 48 weeks ($p < 0.01$ vs baseline; $p < 0.05$ vs control), ↓ new fractures (6.3% at 1 yr vs 31.3% at baseline).	Group A: V.D3 1 µg/day alone.	Combination therapy with etidronate + V.D3* significantly inhibited bone resorption, improved bone mineral level, and tended to reduce new vertebral fractures.
Kanis *et al.* (2007). Systematic review and cost-utility analysis (42)	Postmenopausal women aged ≥50 years in various European countries, primarily at risk of osteoporotic fractures.	Risedronate; modeled cohort, not a clinical trial — typical dose: 5 mg daily.	Reduction in fracture risk (vertebral, non-vertebral, hip); improved cost-effectiveness profile under specific risk thresholds.	Placebo or no treatment; modeled scenario.	Risedronate (5 mg/day) significantly reduced vertebral fracture risk (RR = 0.33; 95% CI: 0.14–0.80) and was cost-effective in women ≥75 years with prior fractures, with an ICER of £35,000/QALY (95% CI: £25k–£106k).

Langdahl *et al*. (2009). RCT, multicenter, double-blind, double-dummy, active-controlled (43)	Patients with GIO*; postmenopausal women, 67 premenopausal women, 83 men; ≥21 years; on ≥5 mg/day, glucocorticoids for ≥3 months.	TPTD* n = 214; 20 µg/day SC + calcium 1000 mg/day + vitamin D 800 IU/day.	LS* BMD* ↑: +7.8% in postMP* women (vs ALN* +3.7%, p < 0.001); +7.0% in preMP* (vs +0.7%, p < 0.001); +7.3% in men (vs +3.7%, p = 0.03); ↓ new vertebral fractures.	ALN*, n = 213; 10 mg/day PO* + same supplements.	TPTD* significantly increased LS* BMD* and reduced vertebral fracture incidence compared to ALN* in all subgroups; effects were independent of sex or menopausal status.

RIS*: Risedronate. RR*: Relative risk; BMD*: Bone mineral density; MD*: Mean difference; ALN*: Alendronate; ALF*: Alfacalcidol; GC*: Glucocorticoids; CI*: Confidence interval; TPTD*: Teriparatide; OC*: Osteocalcin; P1NP*: Procollagen type I N-terminal propeptide; OR*: Odds ratio; Ca*: Calcium; V.D3*: Vitamin D3; ETD*: Etidronate; IBN/IBA*: Ibandronate; ZOL*: Zoledronic acid; CTx*: C-terminal telopeptide; NTx*: N-Terminal Telopeptide; BSAP*: Bone-specific alkaline phosphatase; b-CTx: Beta-CrossLaps; AF*: Alkaline phosphatase; GIOP*: Glucocorticoid-induced osteoporosis; NaF*: Sodium fluoride; BID*:_Twice daily; NS*: Not significant; CKD*: Chronic kidney disease; aVD*: Active vitamin D; S-NTX*: Serum N-terminal telopeptide of type I collagen; ALP*: Bone alkaline phosphatase; PO*: Per os (oral administration); mo*: months; PTH (1–34)*: Parathyroid hormone; SC*: Subcutaneous; TBS*: Trabecular bone score; QCT*: Quantitative computed tomography; DXA*: Dual-energy X-ray absorptiometry; HRT*: Hormone replacement therapy; ROC*: Receiver operating characteristic curve; AUC*: Area under the curve; FEA*: Finite element analysis; NA*: Not applicable; SLE*: Systemic lupus erythematosus; Tb.Sp*: Trabecular separation; RCT*: Randomized controlled trial; sRANKL*: Soluble RANK ligand; IL-6*: Interleukin-6; LS*: Lumbar spine; DMAb*: Denosumab; PPI*: Proton pump inhibitor; MDCT*: Multidetector-row computed tomography; BV/TV*: Bone volume over total volume; SMI*: Structure model index; BTMs*: Bone turnover markers; MIN-M*: Minodronate; TRACP-5b*: Tartrate-resistant acid phosphatase 5b; HR*: Hazard ratio; FN*: Femoral neck; PSL*: Prednisolone; UD*: Ultra-distal radius; YAM*: Young adult mean; postMP*: Postmenopausal; preMP*: Premenopausal; NMA*: Network meta-analysis; SUCRA*: Surface under the cumulative ranking curve; RAL*: Raloxifene; SMD*: Standardized mean difference; CT*: Calcitonin.

Source: Own elaboration.

After reviewing the efficacy of pharmacological therapies in the treatment of glucocorticoid-induced osteoporosis, it is equally important to analyze their effectiveness in clinical practice.

Karras *et al*. conducted an observational study to evaluate the effectiveness of teriparatide in postmenopausal women with severe osteoporosis undergoing glucocorticoid treatment over a 36-month period. This prospective cohort study allowed for the observation of changes in fracture incidence and patient quality of life in a routine clinical setting. To analyze the results, the authors used a logistic regression model with repeated measures to examine changes in fracture risk over time. Compared to the first six months of treatment, fracture risk decreased by 81% between 24 and 30 months and by 89% between 30 and 36 months (p < 0.05). Additionally, reductions in lumbar pain were assessed using a mixed-effects repeated measures model, adjusted for variables such as baseline pain levels and fracture history. Throughout the study, patients reported an improvement in their health-related quality of life (HRQOL), measured using the EQ-5D scale (a standardized instrument for assessing five dimensions of health-related quality of life), with benefits persisting even after discontinuing teriparatide (44). The effectiveness findings are summarized in table 2.

Table 2. Summary of the included studies on real-world effectiveness of treatments for glucocorticoid-induced osteoporosis

Author, year, and study design	Population and age	Intervention (name), n, and dose	Intervention outcome	Comparator (name), n, and dose	Main outcome
Karras *et al.* (2012). Prospective, multinational, observational study (EFOS: european forsteo observational study) (44)	Postmenopausal women with GIO* age: 69.9 years; non-users mean age: 71.2 years.	Teriparatide n = 1581 GC* users; Dose: 20 µg SC* once daily, self-administered.	In GC* users: 16.7% experienced ≥1 fracture over 36 months (69 total fractures); adjusted odds of fracture reduced by 81% (24–30 mo) and 89% (30–36 mo*) vs first 6 mo* ($p < 0.05$). Significant reductions in back pain VAS* and improvements in EQ-5D*, HRQOL* during and after treatment.	No active comparator (observational study). Compared outcomes between GC users (n = 294) vs nonusers (n = 1287). Both groups followed for 36 months.	In GC* users, TPTD* treatment led to a significant reduction in clinical fractures over 36 months, with an 81% and 89% decrease in adjusted odds at months 24–30 and 30–36, respectively ($p = 0.028$). Fracture incidence was 16.7% (49/294). Back pain improved significantly, with a mean VAS* reduction of −22.0 mm ($p < 0.001$), and days in bed due to back pain decreased from 6 to 5 days. EQ-VAS* scores increased by +12.1 points, and EQ-5D* HSV* rose from 0.516 to 0.691 ($p < 0.001$). These benefits were sustained after teriparatide discontinuation. Similar trends were observed in non-GC* users (fracture rate: 12.4%), with slightly greater HRQOL* improvements.

GIOP*: Glucocorticoid-induced osteoporosis; GC*: Glucocorticoids; SC*: Subcutaneous; VAS*: Visual analog scale; EQ-5D*: EuroQol 5 dimensions; HRQOL*: Health-related quality of life; TPTD*: Teriparatide; EQ-VAS*: EuroQol visual analog scale.

Source: Own elaboration.

Safety is also a fundamental aspect when evaluating pharmacological therapies used for the treatment of glucocorticoid-induced osteoporosis. Since these patients often require long-term treatment, it is crucial that medications are not only effective but also have a favorable safety profile. The studies we identified in this review assessed both efficacy and safety parameters. In total, five studies were reviewed. Below, we summarize the main findings, highlighting improvements in bone mineral density, reductions in fracture incidence, adverse effects, and treatment tolerability across different clinical contexts. Safety and efficacy outcomes of the included studies are summarized in table 3.

First, Cauza *et al*. evaluated intravenous pamidronate every three months in postmenopausal women and patients with GIOP. The treatment resulted in a significant increase in lumbar spine BMD in the postmenopausal group ($p < 0.0001$); however, in the GIOP group, no significant changes were observed in this region ($p = 0.724$). Nevertheless, an improvement in BMD at Ward's triangle was recorded in the GIOP group ($p = 0.0029$). In terms of safety, pamidronate was well tolerated, with no serious adverse events. However, minor side effects such as abdominal pain, headache, and mild liver abnormalities were reported, suggesting a generally favorable safety profile, though caution is advised for patients with a history of gastrointestinal or liver conditions (45).

On the other hand, Tanaka *et al*., in the TOWER-GO study, compared weekly teriparatide with weekly alendronate in Japanese patients with GIOP. After 72 weeks, both treatments significantly increased lumbar spine BMD (teriparatide: 5.09% and alendronate: 4.04%; both $p < 0.05$), although teriparatide showed greater increases in bone formation markers. Regarding safety, both groups reported side effects such as nausea, muscle pain, and flu-like symptoms, but there were no significant differences in the frequency or severity of these events between the groups, indicating that both treatments were safe and well tolerated (46).

Fujieda *et al*., in the RISOTTO study, investigated risedronate in patients with GIOP and rheumatoid arthritis. The results showed a 3.49% increase in lumbar spine BMD in the risedronate group, compared to 0.12% in the placebo group ($p < 0.0001$). In terms of safety, 28 patients experienced adverse events, none of which were severe. The most common side effects were mild gastrointestinal discomfort and abdominal pain, which are characteristic of bisphosphonates. Additionally, 10 non-traumatic vertebral fractures were reported, highlighting the need for close monitoring of bone response in these patients (47).

Kitazaki *et al*. compared alendronate with alfacalcidol in patients with GIOP and ulcerative colitis. At the end of the study, alendronate showed a significant increase in lumbar spine BMD and a reduction in bone resorption markers, while both treatments were well tolerated. However, as a bisphosphonate, alendronate has a safety profile that requires particular attention in patients with a history of gastrointestinal conditions due to its potential to cause esophageal irritation. No serious adverse events were reported in this study, nor were treatments discontinued due to side effects, suggesting adequate safety in patients with comorbidities (48).

On the other hand, Glüer *et al*., in the EuroGIOPs study, compared daily teriparatide with weekly risedronate in men. Both treatments had comparable safety profiles, although 10.6% of patients in the risedronate group experienced new clinical fractures, while none of those in the teriparatide group experienced such events. Overall, no significant serious adverse events were reported, and both treatments were well tolerated (49).

Similarly, Allen *et al*. conducted a meta-analysis of 27 clinical trials with 3.075 participants, in which bisphosphonates showed no significant differences in the rate of serious adverse events compared to the control group. In the bisphosphonate group, the incidence of serious events was 14.7% (136 out of 892), compared to 16.2% (131 out of 811) in the control group, with an absolute risk difference of 0% (95% CI: −2% to +2%). The rate of treatment withdrawal due to adverse effects was 7.7% in the bisphosphonate group versus 7.3% in the control group, with a difference of +0.4% (95% CI: −1% to +3%). The most common adverse effects included gastrointestinal discomfort and flu-like symptoms, both considered mild (50).

Similarly, in the HORIZON study, Reid *et al*. compared zoledronic acid and risedronate over one year in 833 patients. Zoledronic acid caused a higher incidence of transient effects (fever and myalgia) within the first three days post-infusion, affecting 27.7% of patients (115 out of 416) compared to 12% (50 out of 417) in the risedronate group. Serious events were rare in both groups, including worsening of rheumatoid arthritis in the treatment group and persistent fever in the prevention group. Regarding renal function, potential increases in creatinine were monitored in the zoledronic acid group, but no clinically significant changes were found (51).

In another study, Nanki *et al*. found that weekly teriparatide was superior to continuous bisphosphonates in patients with GIOP. Teriparatide significantly increased lumbar spine BMD by 4.7% versus 0.8% with bisphosphonates ($p = 0.014$) and also reduced the incidence of new fractures (17.6% vs. 22.7%). However, the teriparatide group reported more adverse effects (42.9% vs. 9.5%), including nausea, headache, and fatigue (52).

Ringe *et al*. evaluated ibandronate compared to alfacalcidol, highlighting that ibandronate was well tolerated and had a lower incidence of hypercalcemia or hypercalciuria (1.9% vs. 7.6%). Only one patient in the ibandronate group discontinued treatment due to a mild adverse event (11).

Meanwhile, Campbell *et al*. analyzed etidronate and calcium in asthmatic patients undergoing glucocorticoid treatment. Etidronate increased lumbar spine BMD by 4.1% ($p = 0.001$) and reduced fractures in postmenopausal women (OR 0.39, 95% CI 0.14-0.99). Regarding safety, the combination of etidronate with calcium increased gastrointestinal side effects (53). In another study in 2009, Campbell *et al*. compared hormone replacement therapy (HRT) with etidronate in postmenopausal women with asthma. Both treatments increased BMD by approximately 1% annually; however, 50% of patients with X-rays developed asymptomatic fractures, limiting their effectiveness in fracture prevention (54).

Finally, Sato *et al*. evaluated etidronate in Japanese patients with connective tissue diseases, showing a 4.8% increase in lumbar spine BMD at 144 weeks ($p < 0.005$), with no new vertebral fractures and minimal adverse effects, highlighting its safety profile (55).

In summary, the reviewed studies indicate that bisphosphonates, teriparatide, and etidronate are effective and generally well-tolerated treatments for glucocorticoid-induced osteoporosis, with acceptable safety profiles. Each treatment has specific adverse effects, with gastrointestinal symptoms being more common with bisphosphonates, while transient effects such as fever and flu-like symptoms are observed with teriparatide and zoledronic acid. Although some treatments, such as teriparatide, may be associated with transient side effects, including post-infusion fever or hypercalcemia, most adverse events are not severe. This reinforces the long-term safety of these treatments for managing GIOP.

Table 3. Analysis of included studies on safety and efficacy in glucocorticoid-induced osteoporosis

Author, year, and study design	Population and age	Intervention, n, and dose	Comparator, n, and dose	Efficacy outcome	Safety outcome
Ringe *et al.* (2003). Randomized clinical trial (11)	Men and women with GIO*. Mean age: 64 years. n = 115 patients.	Intravenous Ibandronate 2 mg every 3 months + calcium 500 mg daily, n = 58.	ALF* 1 µg daily (n = 57) + Ca 500 mg daily.	BMD* after 3 years: Lumbar spine: +13.3% (IBAN*) vs. +2.6% (ALF*) (p < 0.001). Femoral neck: +5.2% (IBAN*) vs. +1.9% (ALF) (p < 0.001). Reduction in vertebral fractures: 8.6% (IBAN*) vs. 22.8% (ALF*) (p = 0.043). Less height loss: −0.7 cm (IBAN*) vs. −1.4 cm (ALF*)(p = 0.001).	Generally, well tolerated. Adverse events: 36 in both groups. More cases of hypercalcemia with alfacalcidol (8.8% vs. 1.7%). More cases of myalgia/ arthralgia with ibandronate (13.8% vs. 7.0%). One patient discontinued ibandronate due to adverse effects (injection site pain, fever, and myalgia).
Nanki *et al.* (2022). Randomized open-label trial (52)	Patients with GIO*. Conducted across 23 centers in Japan. Mean age: 68.2 years. n: 44.	Teriparatide 56.5 µg, once-weekly n = 21.	Bisphosphonates various types and doses, n = 22.	Lumbar spine BMD* increased more with TPTD* vs. BPs* (4.1% vs. 0.5% at 72 weeks, p = 0.209). Proximal femur BMD* change was not significantly different. Incidence of new fractures was lower with TPTD* (11.8% vs. 18.2% at 72 weeks and 17.6% vs. 22.7% at 144 weeks).	Adverse events occurred in 74% of patients. More adverse events with teriparatide (nausea, headache, dizziness, fever, fatigue). Total serious adverse events: 21 (15 in bisphosphonate group, 6 in teriparatide group). Hypercalcemia occurred in one patient receiving teriparatide.

Campbell *et al.* (2004). Randomized controlled trial (53)	Postmenopausal women and men with asthma receiving long-term oral/inhaled GC*. Conducted across 39 chest clinics in the UK*. Age range: 50–70 years. n = 349.	ETD* 400 mg/day for 2 weeks every 3 months + Ca* 500 mg/day, n = 88. ETD* 400 mg/day for 2 weeks every 3 months, n = 81. Ca* 500 mg/day, n = 85.	No treatment, n = 95.	No significant reduction in fracture rates among the treatment groups. ETD* increased lumbar spine BMD* by 4.1% over 5 years (p = 0.001). No significant effect on proximal femur BMD*. Post hoc analysis: Fracture incidence was lower in women receiving ETD* (OR 0.39, p = 0.02).	More adverse effects in etidronate-treated groups (29/147 vs. 5/161 in non-etidronate groups, p = 0.001). Adverse effects included indigestion, nausea, vomiting, diarrhea, and headaches. Higher dropout rates due to side effects in the etidronate + calcium group.
Sato *et al.* (2003). Randomized prospective study (55)	Japanese patients with connective tissue diseases on GC* therapy. Age range: 21–73 years. n = 102.	ETD* 200 mg/day for 2 weeks every 3 months + Ca* 3.0 g/day + ALF*: 0.75 µg/day, n = 51.	Ca* 3.0 g/day + ALF* 0.75 µg/day, n = 51.	Lumbar spine BMD* increased significantly in the ETD* group at 144 weeks (4.8% vs. 0.4%, p < 0.01). Postmenopausal women showed the greatest improvement in BMD* (10.1% vs. 1.35%, p < 0.05). No new vertebral fractures in the ETD* group vs. 2 fractures in the control group.	Two patients in the etidronate group withdrew due to adverse events (headache and facial rash). No gastrointestinal side effects were reported.
Cauza *et al.* (2004). Prospective observational study (45)	Austrian women in postmenopausal group: Mean age: 68.1 year and GIO* group: Mean age: 66.9 years. n = 86.	PAM* 30 mg every 3 months, Ca* 500–1000 mg/day + V.D3*: 250–500 IU/day. n = 86.	N/A	Lumbar spine BMD* significantly increased in postmenopausal osteoporosis (p = 0.000067). No significant change in lumbar spine BMD* in GIO* (p = 0.724). Significant increase in Ward's triangle BMD* in GIO* (p = 0.0029). Decrease in bone turnover markers (alkaline phosphatase and osteocalcin) in postmenopausal osteoporosis.	Well-tolerated with no severe gastrointestinal events. One patient had moderate liver abnormality. One patient experienced abdominal pain while taking NSAIDs.

Fujieda *et al.* (2020). Multicenter, double-blind, randomized, placebo-controlled trial (47)	Patients with AR* and GIO*, Mean age: 70 years. n = 95.	RIS* 75 mg orally, once monthly for 6 months, n = 61.	Placebo, once monthly for 6 months, n = 34.	Lumbar spine BMD* increased significantly in the RIS* group compared to the Placebo group (3.49% vs. 0.12%, $p < 0.0001$). No significant difference in femoral neck or total hip BMD* between groups. Bone turnover markers (TRACP-5b and BAP) decreased significantly with RIS* ($p < 0.0001$). No significant difference in Disease Activity Score (DAS28-ESR) for RA*. Non-traumatic vertebral fractures: 10.7% in RIS* group vs. 11.8% in placebo group ($p = 0.88$).	28 patients experienced adverse events (19 in risedronate, 9 in placebo). No serious adverse events reported. Upper gastric disorders: 7.9% in risedronate vs. 8.8% in placebo. Eight patients in risedronate group withdrew due to adverse events.
Glüer *et al.* (2013). Randomized, open-label trial (49)	Men with GIO, mean age: 56.3 years n = 92.	TPTD*: 20 µg/day SC. n = 45.	RIS* 35 mg/week oral.* n = 47.	At 18 months: Trabecular BMD* (L1-L3) increased significantly more with teriparatide (16.3% vs. 3.8%, $p = 0.004$). HRQCT* showed greater microstructural improvements with TPTD*. Vertebral strength increased more with TPTD* (26.0%-34.0% vs. 4.2%-6.7%, $p < 0.015$).	Similar adverse event rates between groups. No new fractures in the TPTD* group vs. 5 (10.6%) in RIS*($p = 0.056$). No hypercalcemia cases.
Tanaka *et al.* (2020). Randomized, open-label, multicenter trial (46)	Patients with GIO, mean age: 65.8 years. n = 180.	TPTD*: Once-weekly 56.5 µg/week SC. n = 89.	ALN* Once-weekly, n = 91, 35 mg/week oral.	Non-inferiority of TPTD* vs. alendronate in lumbar BMD* change at 72 weeks was not confirmed. However, both significantly increased BMD* (5.09% vs. 4.04%, $p < 0.05$). Bone formation markers increased with TPTD* and decreased with ALN*.	Similar adverse event rates (~50% of patients in both groups). No significant differences in vertebral or non-vertebral fracture incidence. No severe safety events reported with TPTD*

Kitazaki *et al.* (2009). Randomized trial (48)	Patients with UC* receiving GC*, age range: 17–70 years. n = 39.	ALN* 5 mg/ día, n = 19.	ALF* 1 µg/día, n = 20.	ALN* significantly increased lumbar spine BMD* (4.1% vs. 0.9%, p < 0.05). ALN* significantly decreased bone turnover markers, while ALF* had a limited effect.	No significant difference in adverse events between groups. One withdrawal in each group due to pruritus (ALN*) and muscle pain (ALF*). No new fractures reported in either group.
Allen *et al.* (2016). Systematic review (50)	Patients with GIO*, mean age: varied across studies. n = 3075.	ALN* 5–10 mg/day, n = 1052; RIS* 2.5–5 mg/ day, n = 678; ETD* 200–400 mg/day, n = 385; PAM* 30–90 mg/ month IV, n = 180; IBAN* 150 mg/month oral or 3 mg/ quarter IV, n = 225; CLO* 800–1600 mg/ day oral, n = 225.	Ca* and/ or V.D3*, or placebo, n = 1330.	Bisphosphonates reduced vertebral fractures by 43% (77 per 1000 in control vs. 44 per 1000 in treatment, RR 0.57, 95% CI 0.35–0.91). No significant effect on non-vertebral fractures (RR 0.79, 95% CI 0.47–1.33). Increased BMD* at lumbar spine (3.5%) and femoral neck (2.06%).	No significant difference in serious adverse events or withdrawals due to adverse events. No reports of osteonecrosis of the jaw or atypical femoral fractures. Gastrointestinal symptoms were common but mild.
Reid *et al.* (2009). Randomized, double-blind, double-dummy controlled trial (HORIZON Study) (51)	Patients with GIO*, mean age: 18–85 years. n = 833.	ZOL*, 5 mg IV infusion once yearly, n = 416.	RIS*, 5 mg/day oral. n = 417.	ZOL* was non-inferior and superior to risedronate for increasing lumbar spine BMD* at 12 months in both treatment (4.06% vs. 2.71%, p = 0.0001) and prevention (2.60% vs. 0.64%, p < 0.0001) groups. Higher BMD* increases in total hip and femoral neck with ZOL*	Adverse events were more frequent with ZOL*, primarily transient flu-like symptoms in the first 3 days post-infusion. Serious adverse events included worsening rheumatoid arthritis and pyrexia. No cases of osteonecrosis of the jaw. Renal function was stable.

GIO*: Glucocorticoid-induced osteoporosis; BMD*: Bone mineral density; GC*: Glucocorticoids; UK*: United Kingdom; RA*: Rheumatoid arthritis; UC*: Ulcerative colitis; ETD*: Etidronate; Ca*: Calcium; ALF*: Alfacalcidol; PAM*: Pamidronate; VD3*: Vitamin D3; RIS*: Risedronate; TPTD*: Teriparatide; ALN*: Alendronate; IBAN*: Ibandronate; CLO*: Clodronate; ZOL*: Zoledronic acid; BPs*: Bisphosphonates; HRQCT*: High resolution quantitative computed tomography.

Source: Own elaboration.

In summary, bisphosphonates (risedronate, alendronate, and zoledronate), teriparatide, and denosumab are effective treatments for increasing bone mineral density and reducing fracture risk in patients with glucocorticoid-induced osteoporosis. Teriparatide stands out for its superior ability to promote bone formation and reduce vertebral fractures, while bisphosphonates and denosumab significantly lower the risk of non-vertebral fractures. The reviewed therapies have an acceptable safety profile, with mostly mild adverse events. However, it is crucial to consider each patient's individual profile to optimize treatment and minimize risks.

Discussion

Glucocorticoid-induced osteoporosis (GIOP) is a common complication in patients undergoing long-term corticosteroid treatment, typically at doses of ≥5 mg/day for more than 3 months. This condition is associated with a significant loss of bone mineral density (BMD) and an increased risk of fractures, particularly vertebral and hip fractures, which are the most prevalent fracture types in this form of secondary osteoporosis.

This scoping review evaluated the efficacy, effectiveness, and safety of the different available therapies for the treatment of glucocorticoid-induced osteoporosis. Among the most effective treatments are bisphosphonates (risedronate and alendronate) and anabolic agents such as teriparatide, which have demonstrated a significant increase in BMD and a reduction in the risk of both vertebral and non-vertebral fractures.

The reviewed evidence shows a consensus on the use of bisphosphonates as a first-line therapy for fracture prevention in patients with GIOP. In the study by Reid *et al.*, risedronate (5 mg/day) increased lumbar spine BMD by 4.8% and femoral neck BMD by 2.1%, with an 82.4% reduction in the risk of vertebral fractures (6). However, while bisphosphonates remain a cornerstone as a drug class, the clinical use of risedronate has declined in several countries in recent years. In contrast, alendronate and intravenous zoledronic acid continue to be widely used due to their efficacy, dosing convenience, and improved treatment adherence, particularly in patients with contraindications to oral therapy.

This finding is consistent with other studies, such as that by Sambrook *et al.*, which reported a significant increase in lumbar spine BMD with alendronate. Both studies agree that bisphosphonates are effective in preventing vertebral fractures and, to a lesser extent, non-vertebral fractures (including hip and trochanteric fractures) (56).

However, in the clinical trial by Hoes *et al.*, no significant differences were observed in the reduction of new fractures between alendronate and alfacalcidol, suggesting that treatment response may vary depending on the patient's risk profile (7).

Regarding anabolic agents, studies such as Eastell *et al.* showed that teriparatide (20 µg/day) was superior to alendronate in improving BMD and restoring bone formation, particularly in patients with GIOP, who experience greater suppression of bone-forming activity (8). In addition, zoledronic acid deserves specific mention, as evidence from randomized trials (e.g., HORIZON) demonstrates superior or non-inferior improvements in BMD compared with those achieved by oral bisphosphonates, with an acceptable safety profile, making it a valuable option in routine clinical practice.

This study reported a 9.8% increase in lumbar spine BMD and a greater reduction in vertebral fractures. Devogelaer *et al.* also supported the efficacy of teriparatide; however, their analysis found that the glucocorticoid dose influenced treatment response, suggesting that higher corticosteroid doses (>15 mg/day of prednisone) could reduce the effectiveness of BMD improvement. Additionally, safety concerns regarding teriparatide have been raised due to a higher incidence of mild adverse events, such as nausea and fatigue, although serious adverse effects are generally not reported (12).

Limitations and strengths

Although anti-sclerostin agents such as romosozumab were considered within the conceptual framework of this scoping review, no studies meeting the inclusion criteria were

identified specifically for glucocorticoid-induced osteoporosis. This highlights an important evidence gap and the need for future clinical research in this area.

Several limitations were identified in this review, including the heterogeneity of studies in terms of glucocorticoid dose and treatment duration, as well as variability in the studied populations. Differences in inclusion criteria may have influenced comparisons of efficacy and effectiveness outcomes across treatments. Moreover, some studies were not specifically designed to assess fracture prevention, which limits the interpretation of data related to this key clinical outcome. On the other hand, one of the main strengths of this review is the inclusion of recent studies that analyze not only changes in BMD but also bone turnover markers as predictors of therapeutic response, allowing for a more comprehensive approach to evaluating treatment efficacy and safety.

The findings of this review suggest that bisphosphonates, particularly risedronate and alendronate, remain the first-line therapies for preventing vertebral and non-vertebral fractures (mainly hip and trochanteric fractures) in patients with GIOP. However, in patients at higher fracture risk or those with greater suppression of bone formation, teriparatide should be considered a superior therapeutic option. In terms of effectiveness, anabolic agents have been shown to be more effective in improving bone quality, although their use must be weighed against potential adverse effects and the high cost of treatment. Future research should focus on the long-term evaluation of the safety of these treatments, as well as cost-effectiveness studies to assess the incorporation of anabolic agents into the standard treatment of GIOP, given their high cost.

In our review, we identified a notable limitation in the available studies regarding adverse events associated with different drugs used in GIOP. Although some studies mention adverse effects, few delve into the most significant ones or assess their impact on overall patient health. This is concerning, as adverse events can not only limit treatment adherence but also increase the burden of comorbidities in an already vulnerable population.

Conclusion

Glucocorticoid-induced osteoporosis (GIOP) is a treatable complication. Bisphosphonates as a class remain effective options for preventing vertebral and non-vertebral fractures; however, in current clinical practice, alendronate and intravenous zoledronic acid are more commonly used than risedronate in many settings. Anabolic agents, such as teriparatide, represent a valuable alternative for patients at higher fracture risk or with severe suppression of bone formation. Evidence regarding anti-sclerostin therapies (e.g., romosozumab) in GIOP is limited, underscoring the need for future studies to clarify their role. An individualized approach that balances efficacy, safety, availability, and cost-effectiveness is essential.

Author's contribution

Gloria Ibis Tirado Romero: Conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft, and project administration; Juan Felipe Alvarado: Screening, data extraction, validation, and writing – review & editing; Stefany Daniela Mesa Orduz: Investigation and writing – review & editing; Syndi Katherine Guarín Rivera: Data curation, visualization, and resources; Zeyany Vanessa Guerrero Flórez: Supervision, validation, and writing – review & editing.

Ethical statement

The authors declare that this study is a scoping review based exclusively on previously published literature. Therefore, no procedures involving humans or animals were conducted, and no identifiable personal data were used. Accordingly, neither ethics committee approval nor informed consent was required. All studies included in this review had already obtained the corresponding ethical approvals in their original publications.

Conflict of interest

The authors declare no conflicts of interest.

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Use of artificial intelligence (AI)

Artificial intelligence tools were used solely to support language improvement and English style revision during the writing and editing process of the manuscript. The authors were responsible for the conception of the study, literature search and analysis, interpretation of results, and final drafting of the manuscript. Artificial intelligence did not participate in data analysis or in the generation of scientific results.

Data statement

This study is a scoping review based on previously published literature; therefore, no new datasets were generated. The data used were sourced from studies available in scientific databases and can be accessed through the references cited in the manuscript.

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