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Comparative Efficacy of Denosumab and Zoledronic Acid in Osteogenesis Imperfecta: A Meta-Analytic Review

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Abstract

Background: Osteogenesis imperfecta (OI) is a genetic disorder characterized by fragile bones. The condition significantly impacts bone strength. Two commonly used medications are denosumab and zoledronic acid. Denosumab is associated with the risk of hypercalcemia crisis, particularly during treatment initiation. Despite this risk, denosumab has been shown to improve the total hip score. On the other hand, zoledronic acid can cause side effects such as bone pain, fever, and acute-phase reactions.

Methods: We systematically searched electronic databases, including PubMed, Scopus, Elsevier and Cochrane journals, spanning from each database's inception to Aug 26, 2024.Following guidelines specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), Pooled effect estimates with 95% confidence intervals will be calculated using random-effects model**.**

Results: This meta-analysis included two studies with a total of 135 patients, evaluating the safety and effectiveness of Denosumab compared to Zoledronic acid in patients with Osteogenesis Imperfecta. Both studies specifically focused on the occurrence of hypercalcemia crises and included a diverse patient population, encompassing both younger and older individuals. The findings revealed that Denosumab was associated with a higher rate of hypercalcemia crises, while Zoledronic acid demonstrated a broader range of side effects. These results provide insight into the differential impact of these treatments on patient safety across various age groups.

Conclusion: This meta-analysis indicates that Denosumab is associated with a higher rate of uncontrolled conditions and an increased risk of hypercalcemia crisis compared to Zoledronic acid. However, Zoledronic acid demonstrates a higher overall incidence of side effects. Additionally, Denosumab shows a superior total hip score compared to Zoledronic acid. It is important to monitor specific investigations, such as parathyroid hormone (PTH) levels and calcium (Ca) levels, after the administration of both drugs to ensure patient safety and optimize treatment outcomes.

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Introduction

Osteogenesis imperfecta (OI), commonly known as "brittle bone disease," is a genetic disorder that significantly affects bone strength and structure, ranging from mild to severe forms (types I to V). Characterized by bone fragility, recurrent fractures, skeletal deformities and growth retardation, OI also presents with extraosseous manifestations, such as blue sclerosis, osteogenesis imperfecta, joint hypermobility, hearing impairment and cardiovascular complications. One of the main challenges in the management of OI is addressing the low bone mass and weakened bone density associated with the disease. Given the complexity of OI, treatment strategies must balance efficacy and safety.

A clinical trial evaluating denosumab, a monoclonal antibody used to treat osteoporosis, in children with OI was stopped due to the frequent occurrence of hypercalcemia. Therefore, this meta-analysis aims to evaluate the safety and efficacy of Denosumab in adult patients with OI by directly comparing it with zoledronic acid, another commonly used bisphosphonate, to provide information on its benefits and I know the risks.

Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we have conducted systematic searches of electronic databases, including PubMed, Scopus, Cochrane, and Elsevier journals, from the creation of each database until August 26, 2024. Our research strategy includes a combination of relevant keywords and standardized index terms suitable for comparison between effectiveness denosumab and zoledronic acid in young and elderly patients with osteogenesis imperfecta.

SELECTION CRITERIA AND QUALITY ASSESSMENT

- **Type of studies**

This review and meta-analysis will look at studies that watched patients over time or looked back at records. These studies need to have included ten or more people with Osteogenesis imperfecta. The research must compare what happened to patients who took Denosumab versus those who took it. Zoledronic acid. All patients in the studies should have Osteogenesis imperfecta either younger or Older.

- **Types of intervention**

The focus of our study is the use of a Denosumab in patients with a condition called Osteogenesis. imperfecta. We are looking at how Denosumab and Zoledronic acid work in patients with a specific type of condition known as Osteogenesis imperfecta.

- **Types of outcomes measures**

Eligible studies must focus on clinically relevant outcomes regarding the efficacy and safety of Denosumab and Zoledronic acid. These results can include complications such as Bone pain, Fever, Hypercalcemia crisis.

- **Exclusion criteria**

Studies will exclude if they: do not involve human subjects; are not publishing in English; have a sample size smaller than ten in either Denosumab or Zoledronic acid; present overlapping data from the same institution(s); or have a median follow-up duration of less than 6 months. Studies with inadequate reporting of outcomes, such as failing to specify the exact number of events and the total patient-years for comparisons between the Drugs approaches, will be excluding.

Furthermore, studies that do not report outcomes specifically for the effect Denosumab and Zoledronic acid will be excluded. Reviews, case reports, conference abstracts, letters to the editor and editorials will also be excluding. Quality assessment Before conducting the statistical analysis, we assessed the risk of bias and the quality of the included studies. For the two eligible RCTs, we used the revised RoB-2 Cochrane tool and conducted the assessment using Cochrane Review Manager Web.

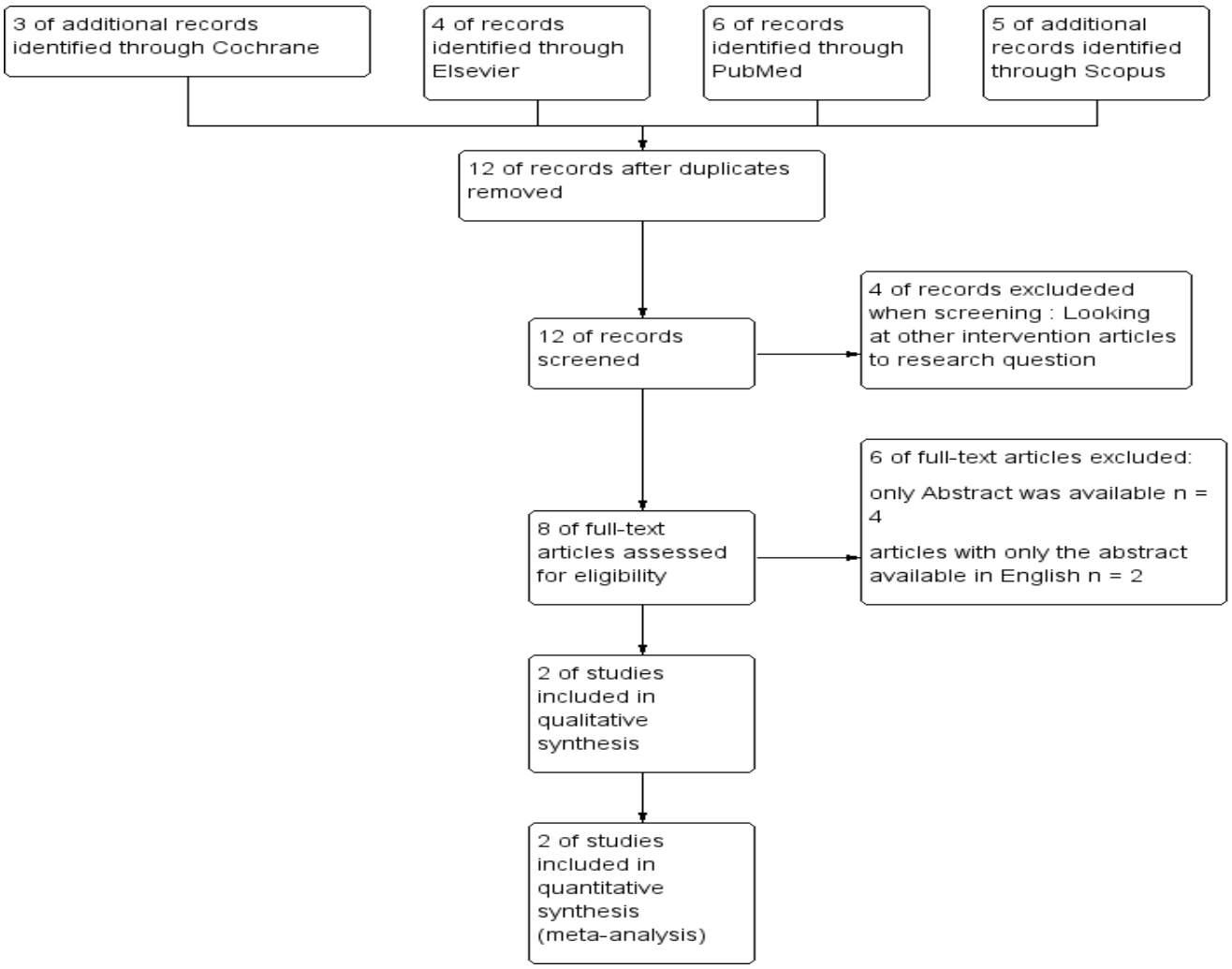

Figure.2: The flowsheet of search results according to PRISMA guidelines.

PRISMA flow diagram provides a detailed account of the selection process for the systematic review and metanalysis on the use of Rituximab and Cyclophosphamide in Patient with the initial search yielded a total of 18 records from various databases: 6 records from PubMed,5 records from Scopus,3 records from Cochrane and 4 additional records identified through Elsevier. After removing duplicates, twelve records remained for further evaluation. The screening process began with these twelve records of which four were excluded for focusing on other interventions or being irrelevant to the research question. This exclusion left twelve records for title screening.

Following this, more record was excluded for Lack of characteristics and has no results. Ultimately, 8 full-text articles were assessed for eligibility, and 2 studies met the inclusion criteria. These two studies were subsequently included in both the systematic review and the quantitative synthesis (metanalysis).

	Sample Size	Study design	Population	Data collection	Outcome
Lin X el at. (China ,2024)	A total of fifty-one adults with OI (denosumab: twenty-five, zoledronic acid: 26)	Randomized controlled trial (RCT)	Patients aged 18 years or older with clinically diagnosed OI were eligible.	Zoledronic acid compared to denosumab.	Denosumab effectively increases aBMD in adults with OI, with similar efficacy to zoledronic acid. Long-term and large-sample studies are needed to confirm the antifracture efficacy and safety of denosumab in adult patients with OI.
Liu J el at. (China ,2024)	Eighty-four children or adolescents with OI (denosumab: forty-two, zoledronic acid: 42)	Randomized controlled trial (RCT)	children and adolescents younger than 18 years old had a history of at least one fracture under minor trauma in childhood.	Zoledronic acid compared to denosumab.	Treatment with denosumab or zoledronic acid is beneficial in increasing BMD and improving the spinal morphometry of children with OI. However, denosumab should be used with caution in pediatric patients with OI because of its common and dangerous side effect of rebound hypercalcemia.

Table 1: summary of the two studies compered (zoledronic acid vs Denosumab)

The (table 1) presents data from four randomized controlled trial conduct in different countries, focusing on the patients with Osteogenesis imperfect. Additions, two studies were focusing on effective and safetyof drugs Jones Lin X el at. (2024) and Liu J el at. (2024). The study by Lin X el at. (2024) involved fifty-one patientsdivided into two groups (25 patients taking Denosumab 60 mg every 6 months) vs 26 patients taking Zoledronic acid 5 mg once for 12 months, were included, of whom forty-nine patients had identified pathogenic mutations, this study included patients aged more than 18 years.

The secondary study Liu J el at. (2024) was focusing on patients who had history of at least one fracture underminor trauma in childhood divided into two groups (42 patients were randomized to receive denosumab subcutaneous injection every 6 months vs 42 patients taken Zoledronic acid intravenous infusion once), thisstudy included patients aged less than 18 years.

Study ID	Drugs	Duration	Number of Patients	Age	Gender	Primary clinical diagnosis				
						Calcium	Cr	ALT	ALP	PTH
Lin X, 2024	denosumab	12 months	25	36.7 ± 12.7	Male11 Female14	2.39 ± 0.08	58.04 ± 14.05	17.00 (12.50-25.50)	85.17 ± 37.39	41.98 ± 13.51
	zoledronic acid		26	37.1 ± 11.8	Male twelve Female fourteen	2.37 ± 0.08	58.08 ± 11.23	19.00 (14.75-34.50)	88.12 ± 36.76	47.08 ± 25.23
Liu J, 2024	denosumab	12 months	42	7.35 (4.16)	Male twenty-seven Female fifteen	2.49 ± 0.09	30 (26, 37)	13 (11, 19)	311 (104)	26.1 (20.3, 31.2)
	zoledronic acid		42	7.57 (4.11)	Male twenty-seven Female fifteen	2.45 ± 0.10	34 (27, 39)	13 (11, 16)	304 (106)	23.3 (16.8, 31.1)

Table. 2 Patients characteristics. (Ca: albumin-adjusted calcium Cr: creatinine ALP: alkaline phosphatase, ALT: glutamic-pyruvic transaminase, PTH: parathyroid hormone).

(Table 2) compare Patient characteristics from two studies. Lin X, 2024 study included 51 patients in Denosumab group 25 patient, range of aged was 36.7 ± 12.7 and have number of gender (Male 11 + Female 14). while zoledronic acid group have 26 patients, range of aged was 37.1 ± 11.8 and have. number of gender (Male 12 + Female 14), this study had different primary clinicals diagnosis (examples Ca 2.39 ± 0.08, Cr 58.04 ± 14.05, ALT 17.00 (12.50-25.50), ALP 85.17 ± 37.39 and PTH 41.98 ± 13.51) these were for patients taking denosumab groups, also. patients taking zoledronic acid groups were Primary clinical diagnosis (Ca 2.37 ± 0.08, Cr 58.08 ± 11.23, ALT 19.00 (14.75-34.50), ALP 88.12 ± 36.76 and PTH 47.08 ± 25.23).

Liu J, 2024 consisted of patients receiving denosumab 42 patients, range of aged 7.35 (4.16) and have number of gender (Male 27+ Female15). while zoledronic acid group have 42 patients, range of aged was 7.57 (4.11) and have number of gender (Male 27 + Female 15). This study had different primary clinicalsdiagnosis for denosumab group (Ca 2.49 ± 0.09, Cr 30 (26, 37), ALT 13 (11, 19) ALP 311 (104) and PTH 26.1 (20.3, 31.2)). in additional the group were taking zoledronic acid had Primary clinical diagnosis (Ca2.45 ± 0.10, Cr 34 (27, 39), ALT 13 (11, 16) ALP 304 (106) and PTH 23.3 (16.8, 31.1)).

In Lin X, 2024 study was older patients and Female more than Male, Liu J, 2024 consisted of patients receiving two drugs were younger patient and Male more than Female, two studies were duration 1

years.

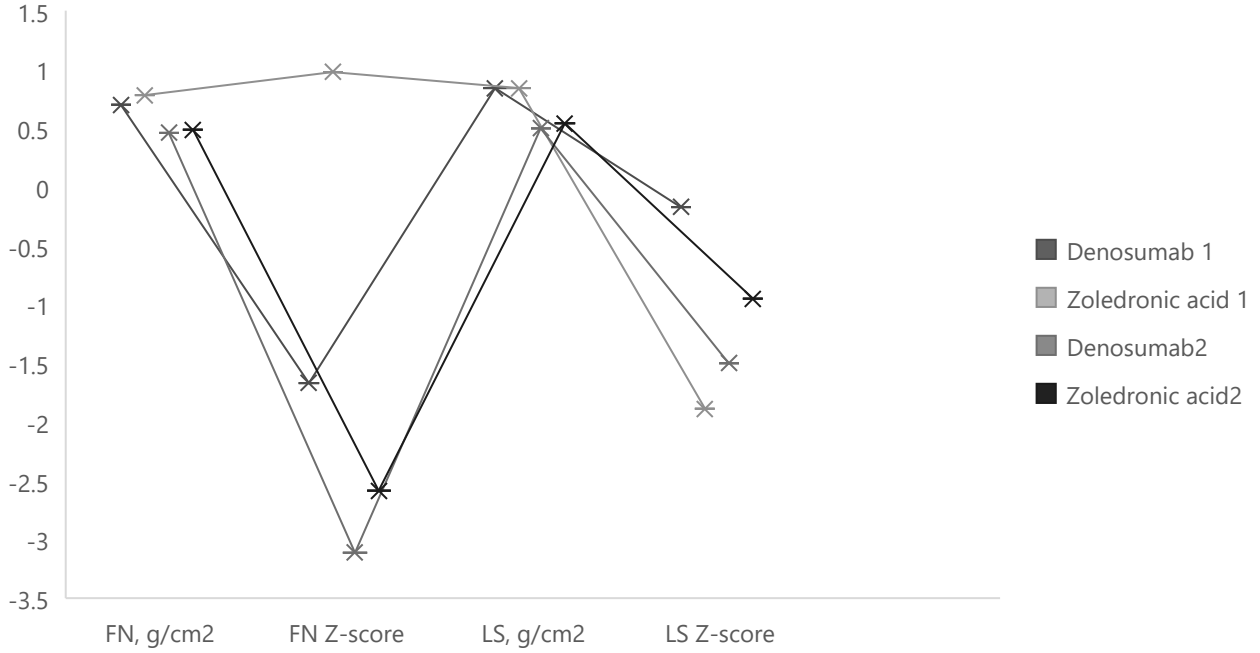

Figure 2: Scores (FN: Femoral neck, LS: lumber spine) in Studies for Denosumab and Zoledronic acid.

This image is showing scores for patients with Osteogenesis imperfecta in two study, Lin X (2024) is representing number 1 and Liu J, 2024 is represent number 2, scores is considering for patients with osteogenesis imperfecta (FN: Femoral neck, LS: lumber spine) in additional z-score for each measure.

The Lin X (2024) has (lumbar spine g/cm^2 0.84 ± 0.22 for Denosumab, lumbar spine g/cm^2 0.84 ± 0.13 forZoledronic acid, lumbar spine Z-score −2.17 ± 1.77 foe Denosumab, lumbar spine Z-score −1.89 ± 1.15 for Zoledronic acid) while Femoral neck (g/cm^2 0.70 ± 0.18 for Denosumab , g/cm^2 0.78 ± 0.15 for Zoledronic acid, Z-score −1.67 ± 1.47for Denosumab, Z-score −0.98 ± 1.19 for Zoledronic acid), after 1 year showed a trend toward higher increases in FN and LS for Patient taken Zoledronic acid.

The Liu J (2024) has (lumbar spine g/cm^2 0.500 for Denosumab , lumbar spine g/cm^2 0.541for Zoledronicacid , lumbar spine Z-score −1.501 for Denosumab , lumbar spine Z-score −0.953 for Zoledronic acid) while Femoral neck (g/cm^2 0.461 for Denosumab , g/cm^2 0.487 for Zoledronic acid , Z-score −3.112 for Denosumab , Z-score −2.587 for Zoledronic acid), after 12 months showed a trend toward higher increases in FN and LS for Patient taken Zoledronic acid higher than Patients taken Denosumab.

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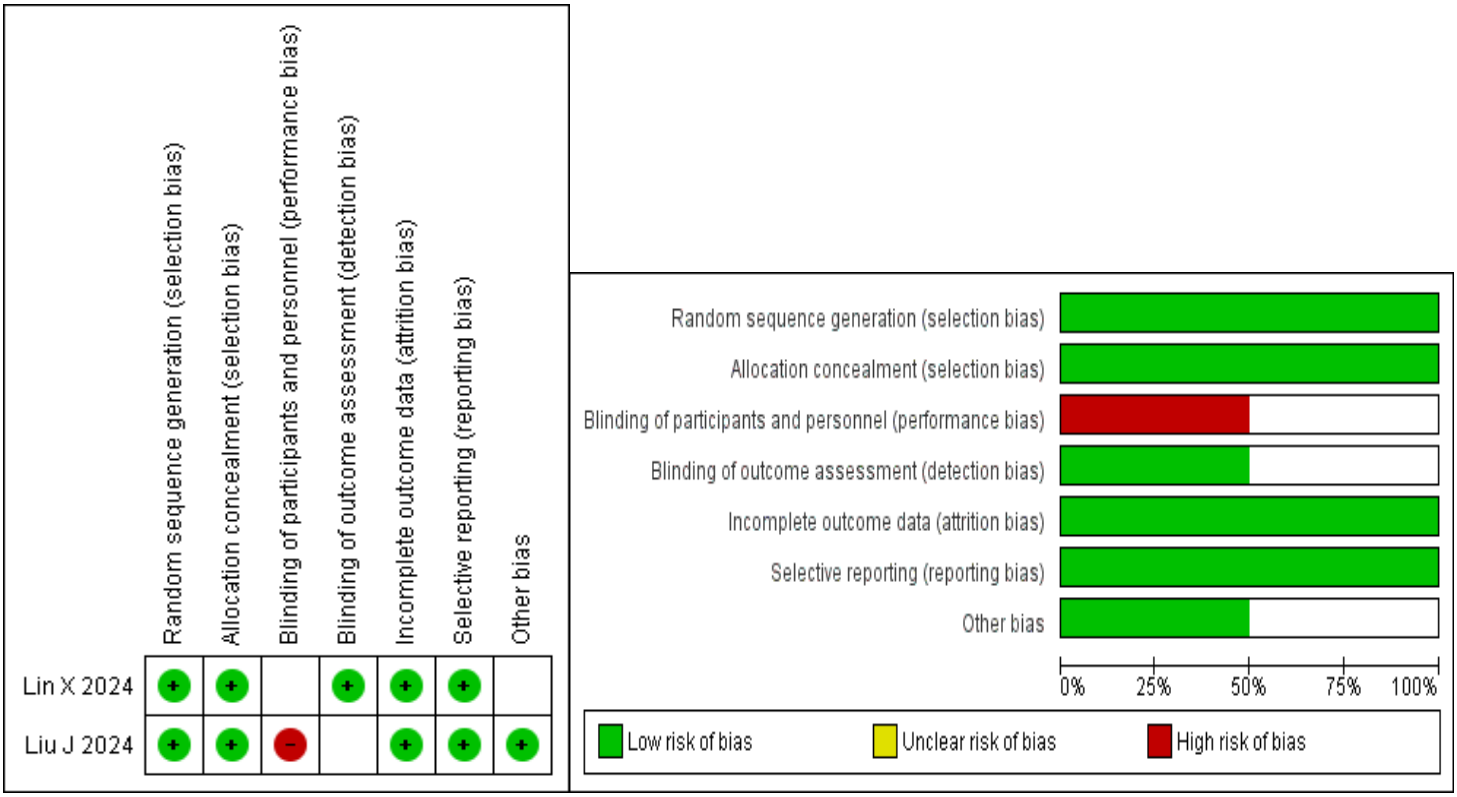

Figure 3: Risk of Bias Assessment using RoB-2 Cochrane tool.

The risk of bias assessment for systematic review and meta-analysis on the use of denosumab versus zoledronic acid in patients with osteogenesis imperfecta includes evaluation of two studies: Lin X (2024), Liu J (2024). The assessment shows that all studies are at insignificant risk of bias in most categories, such as selection, performance, disclosure, attrition and reporting bias, except for blinding of participants and staff (selection bias) in the study of Liu J (2024) which was high risk because it was open. Key areas such as random sequence generation, allocation concealment, hosting and data reporting were consistently rated as minimal risk, reflecting a robust methodology.

This consistent assessment of negligible risk in these key areas suggests that the individual studies were conducted using robust methodology, minimizing the risk of biased results. In the overall evaluation of the studies, many categories continue to reflect the minimal risk of bias. Random sequence generation, allocation concealment, incomplete outcome data, selective reporting,and other biases were all reported with 92% insignificant risk.

However, some concerns were noted in the categories of performance bias and detection bias, where approximately 21% of the assessments indicated an unclear risk of bias and 7% of the assessments indicated an elevated risk of bias. This ambiguity arises from the blinding of participants and personnel and the blinding of outcomeassessment, which are crucial for preventing performance and detection biases. Overall, the studies demonstrate a strong methodological quality with minimal risk of bias, lendingcredibility to the findings of the systematic review and metanalysis. Despite the minor concerns inperformance and detection biases, the predominance of low-risk ratings supports the validity and reliability of the conclusions drawn regarding the effectiveness of the Denosumab compared Zoledronic acid in patients with Osteogenesis imperfecta.

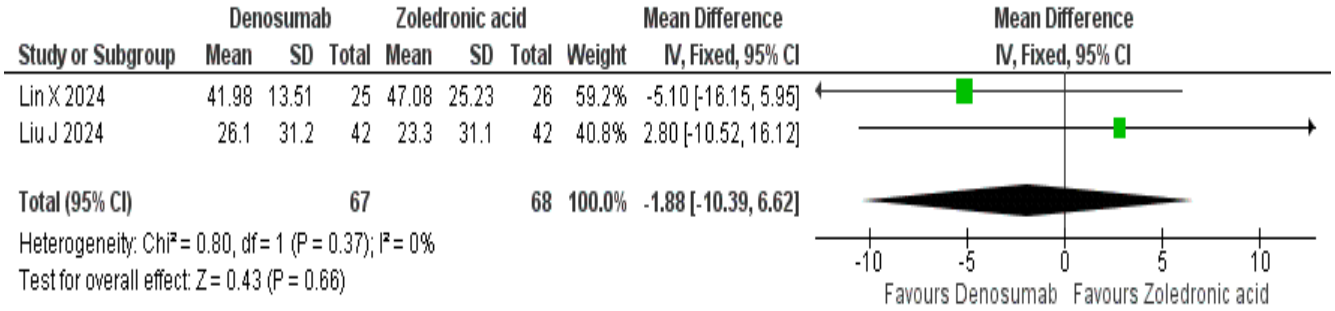

Figure 4: The forest plot of the Parathyroid Score for Osteogenesis imperfecta of the two included studies using a fixed-effects model.

This image is a forest plot from a meta-analysis comparing effectiveness between two drugs. (Denosumab versus Zoledronic acid) in patient with Osteogenesis imperfecta: It includes data from two studies, " Lin X 2024, Liu J 2024 ". For each study, the mean, standard deviation (SD), and total number of participants in both Denosumab and Zoledronic acid groups are listed.

The mean difference between these groups, along with the 95% confidence interval (CI), is provided for each study. The inverse variance method (IV) and a Fixed-effect model (Fixed) were used to calculate these differences. The weight assigned to each study in the meta-analysis is based on the sample size and variance. The Chi-square (Chi^2) test for heterogeneity assesses whether the differences in results across studies are due to chance, with a p-value of 0.66 and I^2 of 0% indicating no heterogeneity.

The overall mean difference between the Denosumab and Zoledronic acid do not favor (pooled effect size -1.88 ,95%Cl [- 10.39 to 6062], P=0.66. Pooled studies were homogenous (chi 0.8, p=0.37, I=0%).

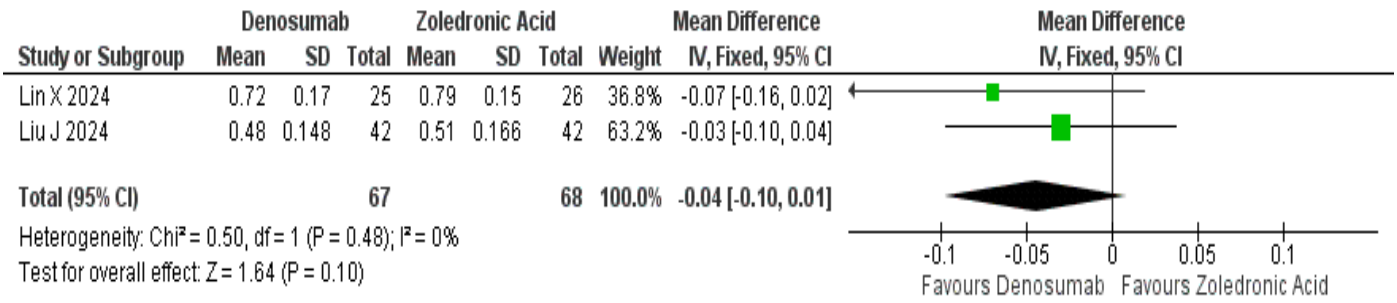

Figure 4: The forest plot of the Total hip Score for Osteogenesis imperfecta of the two included studies using a fixed-effects model.

This image is a forest plot from a meta-analysis comparing effectiveness in Total hip between two drugs (Denosumab vs Zoledronic acid) in patient with Osteogenesis imperfecta: It includes data from Two studies," Lin X 2024, Liu J 2024 " For each study, the mean, standard deviation (SD), and total number of participants in both Denosumab and Zoledronic acid groups are listed.

The mean difference between these groups, along with the 95% confidence interval (CI), is provided for each study. The inverse variance method (IV) and a Fixed-effect model (Fixed) were used to calculate these differences. The weight assigned to each study in the meta-analysis is based on the sample size and variance. The Chi-square (Chi^2) test for heterogeneity assesses whether the differencesin results across studies are due to chance, with a p-value of 0.10 and I^2 of 0% indicating no heterogeneity.

The overall mean difference between the Denosumab and the Zoledronic acid favored the Denosumab (pooled effect size -0.04 ,95%CI [-0.10 to 0.01], P=0.10. Pooled studies were homogenous (chi=0.50, p=0.48, I=0%).

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Discussion

In Our meta-analysis, we included all studies that compared between two drugs (Denosumab versus Zoledronic acid) in patients with Osteogenesis imperfect. We focus on older and younger patient with osteogenesis imperfecta, and we evaluated the two drugs by Total hip and Parathyroid scores. In addition, side effects for each drug. Also, we considered studies that patient developed hypercalcemia crisis. Our analysis included critical investigations in patients with Osteogenesis imperfecta such as Ca (Ca, calcium),ALT (ALT, alanine aminotransferase), LS (Lumbar spine) AND FN (Femoral neck).

Therefore, The Doctors must be careful ensure of investigations After give any drugs for patient with Osteogenesis imperfecta study found that Denosumab has safety and efficacy on children with Osteogenesis imperfecta causes an increase in aBMD and Z-score and improves the spinal morphometry of children with Osteogenesis imperfecta, as supported by two studies. Also, these studiesshow that Denosumab has adverse effects lower than zoledronic acid.

These studies indicated that Denosumab scores higher on Calcium (has effect on developed hypercalcemia crisis patient with Osteogenesis imperfecta). Conversely, zoledronic acid was associated with a higher risk of bone pain,Fever.Although patients with osteogenesis imperfecta have increased skeletal fragility and a high risk of fracture throughout life, treatment is often neglected in elderly patients with osteogenesis, because the risk of fracture generally decreases in middle age. Therapeutic studies are rare in adult patients with osteogenesis, but denosumab has been shown to reduce bone resorption, increase BMD and reduce fracture risk. targeting the bone resorption mediator RANKL.

Using the parathyroid score for patients with osteogenesis imperfecta, two studies reported effect sizes-1.88, with a preference between denosumab and zoledronic acid (elevated serum calcium activates negative feedback mechanisms, thus inhibiting further release of PTH and reducing PTH levels. However, a previous study showed that the overall incidence of hypocalcemia during denosumab treatment was low. These studies highlight the complexity of choosing the most appropriate treatment and suggest that the decision should be adapted to the individual profiles of patients in terms of safety and efficacy, in two studies focused on patients with osteogenesis imperfecta. On the other hand, denosumab was discovered uncontrolled in three patients after its use, and zoledronic acid was controlled for all patients with osteogenesis imperfecta.

Conclusion

Our systematic review and meta-analysis revealed a clinically significant reduction in adverse effects and effectiveness of the use of Denosumab and Zoledronic acid in patient Osteogenesis imperfecta. These findings are particularly relevant. When treating Osteogenesis imperfecta with Denosumab andZoledronic acid, we aimed in our meta-analysis to determine which drug is more effective and safer forpatients with OI. Our Research has indicated that Denosumab is associated with higher hypercalcemiacrisis rates and less control over the disease compared to Zoledronic acid. On the other hand, Zoledronic acid has significant adverse effects (bone pain, fever). Therefore, we will be careful consideration is required when selecting the appropriate treatment for patient with renal disease tobalance efficacy and minimize harmful consequences.

Limitations of the study

The heterogeneity of treatment in patients with Osteogenesis imperfecta included in assorted studies makes it challenging to draw definitive conclusions about the Denosumab and Zoledronic acid efficacyacross the spectrum of these complex cases. Future research focusing on compared by effectiveness between Denosumab and Zoledronic acid would provide more targeted insights into the benefits andlimitations of the drugs in these distinct scenarios. It is important to note that this meta-analysis only included two studies specifically investigating Vertebral compression fracture (VCF) and TBS. This limited sample size restricts the statistical power of the analysis and underscores the urgent need foradditional research in this area to confirm these preliminary findings and establish more definitive conclusions.

Declarations of interest

None.

Ethical approval

This meta-analysis was based on previous published studies; thus, no ethical approval and patient consent are required.

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