



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغييرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



HANAA ALY



**Comparative Study between the use of
Denosumab and Zoledronic acid in
Treatment of Giant Cell Tumor of Bone
(A Systematic Review and Meta-Analysis)**

Thesis

For Partial Fulfilment of Master Degree
in Orthopedic Surgery

By

Mohamed Samir Elsayed Fuda

M.B.B.Ch.,

Faculty of Medicine - Ain Shams University

Under Supervision of

Prof. Dr. Mohamed Abdel Rahman Mostafa

Professor of Orthopedic Surgery

Faculty of Medicine - Ain Shams University

Dr. Sherif Ishak Azmy

Assistant Professor of Orthopedic Surgery

Faculty of Medicine - Ain Shams University

*Faculty of Medicine
Ain Shams University*

2021

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببنا أنك لا تعلم لنا
إلا ما علمتنا أنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgment

*First and foremost, I feel always indebted to **ALLAH**, the Most Kind and Most Merciful.*

*I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Mohamed Abdel Rahman Mostafa**, Professor of Orthopedic Surgery - Faculty of Medicine- Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

*I am also delighted to express my deepest gratitude and thanks to **Dr. Sherif Tshak Azmy**, Assistant Professor of Orthopedic Surgery, Faculty of Medicine, Ain Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Mohamed Samir Elsayed Fuda

List of Contents

Title	Page No.
List of Tables	5
List of Figures	6
List of Abbreviations.....	8
Introduction	1
Aim of the Work.....	3
Review of Literature	
▪ Giant Cell Tumor of Bone.....	4
▪ Treatment of GCT	16
Materials and Methods	27
Results	30
Discussion	43
Summary and Conclusion.....	59
Recommendations	61
References	62
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table 1:	Characteristics of included studies	31
Table 2:	Mean age and sex	40
Table 3:	Comparison between both drugs regarding efficacy	42

List of Figures

Fig. No.	Title	Page No.
Figure (1):	High-power histological view of giant cell tumor of bone.....	5
Figure (2):	RANK/RANKL/OPG pathway in norma osteoclastogenesis.....	6
Figure (3):	RANK/RANKL/OPG pathway in giant cell tumor of bone	9
Figure (4):	Anteroposterior radiograph of knee of giant cell tumor of bone.....	12
Figure (5):	Anteroposterior radiograph of knee.....	13
Figure (6):	Coronal T1 knee	14
Figure (7):	Multidisciplinary treatment recommendations for GCT.....	18
Figure (8):	Proposed mechanism of action of denosumab in GCT.....	22
Figure (9):	PRISMA (preferred reporting items for Systematic reviews and Meta-Analyses) flow diaphragm for study selection	30
Figure (10):	Summary of histopathologic results regarding the rate of denosumab from the baseline until the first follow up.	33
Figure (11):	Forest plot: summary of radiologic results regarding the rate of denosumab from the baseline until the first follow up.	34
Figure (12):	Forest plot: summary of pain rate of denosumab from the baseline until the first follow up.....	35

List of Figures cont...

Fig. No.	Title	Page No.
Figure (13):	Forest plot: summary of hypocalcemia rate of denosumab from the baseline until the first follow up.....	36
Figure (14):	Forest plot: overall recurrence.....	38
Figure (15):	Forest plot: Recurrence with primary lesions.....	38
Figure (16):	Forest plots for the effect of ZOLEDRONIC acid on total postoperative recurrence.	39
Figure (17):	Mean age of included studies.....	40
Figure (18):	Sex distribution.....	41
Figure (19):	Comparison between studies regarding drug effectiveness	42

List of Abbreviations

Abb.	Full term
<i>BMPs</i>	<i>Bone morphogenetic proteins</i>
<i>EMA</i>	<i>European Medicines Agency</i>
<i>FGFs</i>	<i>Fibroblast growth factors</i>
<i>GCT</i>	<i>Giant cell tumor of bone</i>
<i>IGFs</i>	<i>Insulin-like growth actors</i>
<i>IKKs</i>	<i>I-KappaB kinases</i>
<i>IL</i>	<i>Interleukin</i>
<i>JNK</i>	<i>c-Jun N-terminal kinase</i>
<i>MAPK</i>	<i>Mitogen-activated protein kinase</i>
<i>MRI</i>	<i>Magnetic resonance imaging</i>
<i>NFATc1</i>	<i>Nuclear factor of activated T cells, cytoplasmic 1</i>
<i>OPG</i>	<i>Osteoprotegerin</i>
<i>PGE2</i>	<i>Prostaglandin E</i>
<i>PMMA</i>	<i>Polymethyl methacrylate</i>
<i>PTHrP</i>	<i>Parathyroid hormone-releasing protein</i>
<i>RANKL</i>	<i>Receptor activator nuclear factor K-B ligand</i>
<i>RT</i>	<i>Radiotherapy</i>
<i>SREs</i>	<i>Skeletal related events</i>
<i>TNF</i>	<i>Tumor Necrosis Factor</i>
<i>TNFR</i>	<i>TNF family receptor</i>
<i>TRAF</i>	<i>Tumor Necrosis Factor Receptor Associated Factors</i>
<i>US FDA</i>	<i>United States Food and Drug Administration</i>

Introduction

Giant cell tumor of bone (GCT) is a benign primary but locally aggressive bone tumor, most commonly occurring in long bones of patients with range of age 30–50 years and might have a tendency to metastasize ^[1]. GCT is composed of reactive multinuclear osteoclast-like giant cells expressing receptor activator of nuclear factor k-B (RANK) and neoplastic mononuclear stromal cells expressing RANK-ligand (RANKL); the latter promotes osteoclast formation, migration, and survival, resulting in bone resorption ^[2].

Preferential treatment is curettage and high speed Burre with local adjuvants including phenol, alcohol or liquid nitrogen, and cavity filling with bone graft and/or poly-methyl-methacrylate (PMMA), with a rate of recurrence ranged between 27-31% ^[3,4]. In more advanced cases, when joint salvage is regarded impossible, en-bloc resection and endo-prosthetic joint replacement is often considered, resulting in decrease of recurrence risks, but high rates of complication and lesser functional outcome. Also, GCT in the axial skeleton and pelvis or other non-long bone localizations are less amenable to non-mutilating surgery and often intra-lesional surgery is the only achievable option surgically ^[5].

The high recurrence risk after intra-lesional surgery in advanced GCT, and subsequent need for (multiple) re-operations and sometimes extensive surgery can result in functional loss in this intermediate but locally aggressive

disease. This major clinical problem resulted in the quest for systemic targeted therapy aiming at the facilitation of less invasive surgery or even replaces surgery in metastatic patients or cases that are not amenable to surgery. Currently, two different drugs are used, first is the recently approved RANKL inhibitor denosumab inhibits recruitment of osteoclast-like giant cells by neoplastic stromal cells and thereby prevents osteolysis; a calcified rim is formed around tumorous soft tissue, facilitating intralesional surgery in previously ‘uncuretable’ GCT ^[6].

Second is the bisphosphonate zoledronic acid (ZA) that may stabilize local and metastatic disease by its apoptotic effect on neoplastic mononuclear cell population in GCT ^[7].

There are still some unanswered questions in the multidisciplinary treatment of GCT ^[8], especially now concerns have arisen on increased recurrence rate, side-effects after prolonged systemic therapy and case reports on secondary malignancy after denosumab. In this regard, optimal treatment dose and duration have not yet been affirmed. Linguistically, these concerns are reflected in titles of scientific articles, shifting from ‘Denosumab: A breakthrough in treatment of GCT?’ ^[9] towards ‘Challenges’ ^[10], ‘Lessons learned from early experience’ ^[11] and ‘Present day controversies’ ^[12]. In addition, due to denosumab’s high efficacy, alternative targeted therapies including directly working zoledronic acid, are studied to a lesser extent.

Aim of the Work

The aim of this study was to review the literature about the use of denosumab vs zoledronic acid in treatment of GCT regarding their efficacy and oncological effects.

Chapter 1**Giant Cell Tumor of Bone****Overview of Giant Cell Tumor of bone**

Giant cell tumor of bone (GCT) is a benign lesion with tendency toward local aggressive invasion but metastases may occur in 1% to 9% of patients and some earlier studies have correlated the incidence of metastases with aggressive growth and local recurrence ^[13].

It accounts for approximately 5% to 6% of primary bone tumors, usually occurs in the meta-epiphyseal region of long bones but may also occur in the axial skeleton or small bones in hands and feet ^[14].

Pathophysiology of GCT

Giant cell tumor of bone has a dark brown-to-reddish appearance that is friable in texture, while the histological appearance of GCT classically reveals numerous large multinucleated giant cells dispersed in the background stroma of mononuclear spindle cells and monocytes. The mononuclear spindle cell can also present plump and epithelioid in shape. The monocyte nuclei have features identical to those of the larger osteoclast-like giant cells, which can contain large numbers of these nuclei [>50] [Figure 1]. ^[15]