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Real World Experience Demonstrating Limited Efficacy of Denosumab in Osteonecrosis of the Hip

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Abstract

Background: Osteonecrosis of the femoral head (ONFH) is a progressive condition that often ends in collapse of the head and necessitates Total Hip Arthroplasty (THA). Drugs intended to preserve the native hip have given inconsistent and variable results. Denosumab is a monoclonal antibody against the receptor activator of nuclear factor-kappa B ligand (RANKL); it blocks osteoclast-mediated bone resorption and has shown promise in experimental work and early clinical reports in the treatment of ONFH. The aim of our study is to evaluate whether denosumab delays radiological progression and reduces the need for THA in patients with ONFH. **Methods:** We retrospectively reviewed patients with Ficat-Arlet Stage I-III ONFH treated with denosumab at a tertiary care centre between January 2019 and December 2022. Those with Stage IV disease, hip arthritis, contraindications to denosumab, or insufficient follow-up were excluded, leaving 17 patients (31 hips) followed for at least three years. Denosumab was given as 120 mg monthly for three months and then 60 mg every six months for three years. Pain and function were tracked with the Visual Analogue Scale (VAS) and Harris Hip Score (HHS), and radiological progression with serial radiographs and MRI. Progression was defined as advancement of the Ficat-Arlet stage and collapse as progression to Stage III or beyond; conversion to THA was treated as treatment failure. **Results:** The mean age was 41.6 years (range, 20 - 58). At presentation, 25 hips (80.6%) were Stage II, five (16.1%) were Stage III, and one (3.2%) was Stage I. The mean VAS decreased from 6.81 at baseline to 5.32 at one year, whereas the mean HHS barely changed, rising from 61.16 to 62.77 over the same interval. Radiological progression was seen in the single Stage I hip (100%), in 10 of 25 Stage II hips (40%), and in three of five Stage III hips (60%). Collapse occurred in 11 hips overall, and nine (29%) hips required THA (clinical failure rate). **Conclusion:** Denosumab did little to prevent radiological progression, collapse, or conversion to THA in this cohort. Pain eased mod-

estly, but functional gains were minimal, and a sizeable proportion of hips progressed despite treatment. On this evidence, denosumab is unlikely to work as a standalone joint-preserving therapy for ONFH, and prospective controlled studies are needed to clarify what role, if any, it has in managing the condition.

Keywords

Avascular Necrosis, Denosumab, Progression, Hip Replacement

1. Introduction

Osteonecrosis of the femoral head (ONFH) is a progressive disorder that often leads to collapse of the head and, in time, to total hip arthroplasty (THA). It begins when the blood supply to the femoral head is compromised, killing osteocytes and leaving the bone to deteriorate structurally. THA gives dependable results in adults with advanced disease, but in younger patients and in early-stage disease, surgeons usually prefer joint-preserving options such as core decompression, corrective osteotomy, and bone grafting. Drug treatments, including bisphosphonates and lipid-lowering agents, have been tried as adjuncts to stave off collapse.

Bisphosphonates and statins have been reported to curb bone resorption and slow the advance of osteonecrotic lesions, but the clinical picture is far from settled. Agarwala *et al.* described less radiographic progression and fewer conversions to surgery with bisphosphonate therapy [1] [2], yet a more recent randomized controlled trial found no meaningful effect on collapse or on the need for THA [3] [4]. A meta-analysis told a similar story: bone-remodelling outcomes improved in animal models, but no consistent clinical benefit emerged [5]. The gap between laboratory promise and clinical reality is exactly why a genuinely effective drug for avascular necrosis is still being sought.

Denosumab, a fully human monoclonal antibody against the receptor activator of nuclear factor-κB ligand (RANKL), is widely used for osteoporosis. It suppresses bone resorption by blocking RANKL-driven osteoclast formation and activity, a route quite different from that of bisphosphonates, and has been reported to help in conditions such as osteogenesis imperfecta and fibrous dysplasia. In animal work, Kim *et al.* found that RANKL inhibition reduced both bone resorption and femoral head deformity after ischaemic osteonecrosis [6], and a recent retrospective comparison reported that denosumab shrank necrotic lesion volume and held back radiographic progression in early-stage AVN [7]. Even so, solid clinical evidence for denosumab in ONFH is conspicuously scarce.

We therefore set out to evaluate what denosumab can offer in the management of osteonecrosis of the femoral head.

2. Materials and Methods

This retrospective study was carried out at a tertiary care hospital in Mumbai,

India, with approval from the Institutional Review Board. We collected data on patients with hip AVN treated with denosumab between January 2019 and December 2022. Patients with hip arthritis, Ficat-Arlet Stage IV AVN, or contraindications to denosumab were excluded. Twenty-three patients (42 hips) with AVN of the femoral head were treated at our centre over this period; three with Stage IV disease were excluded, and three were lost to follow-up, leaving the final cohort.

2.1. Medical Management

Each patient received denosumab 120 mg monthly for the first three months and then 60 mg subcutaneously every six months for three years. All were given daily calcium 1000 mg and vitamin D 400 IU, with analgesics added as required.

2.2. Assessment

Patients were reviewed clinically and radiologically at 6 weeks, 3 months, 6 months, and every 6 months thereafter, for a minimum of three years. At presentation and at each visit, plain radiographs of both hips were taken in anteroposterior and frog-leg lateral views. An independent, blinded radiologist staged the femoral head using the Ficat-Arlet system and recorded staging, progression, and collapse. Progression was recorded whenever the stage moved up during the study period, and collapse whenever a hip reached stage 3 or higher. MRI of both hips and the pelvis was used alongside the radiographs to gauge the resolution of bone marrow oedema.

Clinical outcomes were captured with the VAS and the Harris Hip Score. A hip that progressed to total hip replacement for pain and disability during the study period was counted as a clinical failure.

2.3. Statistical Analysis

Statistical analysis was performed using STATA IC version 13.1 (StataCorp LLC, College Station, TX, USA). Continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are expressed as frequencies and percentages. Changes in Visual Analogue Scale (VAS) and Harris Hip Score (HHS) over serial follow-up visits were analysed using repeated-measures analysis of variance (ANOVA). A p-value < 0.05 was considered statistically significant. Radiological progression, collapse, and conversion to total hip arthroplasty (THA) were summarized descriptively because of the small sample size and the inclusion of bilateral hips in several patients. The hip was considered the unit of analysis. Because several patients contributed bilateral hips, observations were not completely independent. Consequently, the radiological and clinical outcomes should be interpreted as descriptive, and the results should be interpreted with appropriate caution.

3. Results

The 17 patients had a mean age of 41.6 years (range, 20 - 58); 11 were men and

the remainder were women. Fourteen had bilateral AVN (28 hips) and three had unilateral disease (3 hips), giving 31 hips in all. Most hips presented in Ficat-Arlet stage 2 (25 hips, 80.6%); the remaining hips were in stage 3 (five, 16.3%) and stage 1 (one, 3.2%) (Table 1).

Table 1. The radiological stage at presentation and the radiological progression during the follow-up period.

Radiological Stage	At presentation (n = 31)	6 weeks (n = 31)	3 month (n = 31)	6 month (n = 31)	1 year (n = 31)
1	1 (3.2%)	1 (3.2%)	1 (3.2%)	0 (0%)	0 (0%)
2	25 (80.6%)	25 (80.6%)	25 (80.6%)	20 (64.5%)	16 (51.6%)
3	5 (16.2%)	5 (16.2%)	4 (12.9%)	10 (32.3%)	12 (38.7%)
4	0 (0%)	0 (0%)	1 (3.2%)	1 (3.2%)	3 (9.7%)

The mean VAS was 6.81 at presentation and actually rose slightly to 7.06 six weeks into treatment. Pain then began to ease from the three-month mark, and by one year the mean VAS had fallen to 5.32. Sex made no significant difference to this change over time ($p > 0.05$ for the interaction).

Mean HHS was 61.16 at presentation and dipped to 56.39 at 6 weeks before returning to around baseline at 3 months (62.58), 6 months (62.68), and 1 year (62.77). In other words, function showed an early dip, recovered modestly, and then plateaued, with no meaningful gain at the later visits.

By one year, radiological progression had occurred in the single stage I hip (I to II, 100%), in 10 stage II hips (II to III, 40%), and in three stage III hips (III to IV, 60%) (Table 2). The collapse rate was 100% in stage I and 40% in stage II. Nine of the 31 hips (29%) ultimately required total hip replacement (THR) and were classified as treatment failures; six of these were stage 2 and three were stage 3 on the Ficat-Arlet system (Table 3).

Table 2. The stage-wise radiological progression.

Stage	No. of Hips (%)
1 to 2	1 (100%)
1 to 3	0 (0%)
1 to 4	0 (0%)
2 to 3	10 (40.0%)
2 to 4	0 (0%)
3 to 4	3 (60.0%)

Table 3. The stage-wise clinical failure rate.

At Presentation	No. of Hips (%)
Stage-1	0 (0%)
Stage-2	6 (24.0%)
Stage-3	3 (60.0%)

No treatment-related serious adverse events were observed during the study period. No patients developed symptomatic hypocalcaemia, osteonecrosis of the jaw, atypical femoral fractures, severe infections, or other complications requiring discontinuation of denosumab therapy. All patients completed the planned treatment regimen while receiving calcium and vitamin D supplementation.

4. Discussion

ONFH is the most common reason for THA in young adults. Left untreated, the head collapses and surgery becomes unavoidable. THA is among the most cost-effective and reliably successful operations in orthopaedics, yet patients with ONFH are often young and, for a range of reasons, prefer to postpone it.

Management of ONFH currently spans analgesia, protected weight-bearing, medical therapy, and surgery, principally THA. A number of medical options—hyperbaric oxygen, prostaglandin infusions, low-molecular-weight heparin, and statins—have been tried with inconsistent results. The more important step for adults came when Agarwala *et al.* showed that bisphosphonates could be used effectively in AVN of the femoral head [1] [2]. Failure rates with bisphosphonates are low, but patients who do not respond still need an alternative.

Denosumab offers another way to damp down osteoclast activity and bone resorption. As Cummings *et al.* described, it is a fully human monoclonal antibody that binds RANKL and stops it from engaging RANK [8]; osteoclast formation and function fall, resorption drops, and bone density rises. Several groups have shown that denosumab either drives osteoclasts into apoptosis or blocks the maturation of their precursors [9] [10], and some evidence suggests it further restrains osteoclast function by lowering autophagy within these cells [11].

Liu *et al.* suggested that denosumab might limit collapse by suppressing both osteoclast activity and autophagy; in their series, 60 mg given subcutaneously every six months for two years produced favourable radiological outcomes [11]. Our own regimen drew on the well-characterised safety of denosumab at 120 mg every four weeks, the dose routinely used for hypercalcaemia of malignancy and skeletal metastases [12] [13]. Those studies raised no notable safety signals at this dose, which reassured us that it was both standard and well tolerated for our purpose.

The largest clinical experience to date comes from Moon *et al.* [7], who studied 272 hips with symptomatic non-traumatic ONFH. Compared with controls, hips treated with denosumab collapsed less often (24.7% vs. 38.1%) and lost more necrotic lesion volume on MRI. Fewer denosumab patients went on to THA (15.8% vs. 23%), though this difference did not reach significance, and the authors concluded that the drug may delay radiological progression, especially in early disease.

Our results were less encouraging. Forty per cent of Stage II hips progressed and 29% eventually needed THA, while Harris Hip Scores barely shifted over follow-up. Suppressing osteoclast-mediated resorption, it seems, is not by itself

enough to change the natural course of ONFH. Why our outcomes diverged from those of Moon *et al.* is hard to pin down, but differences in patient selection, lesion characteristics, symptom duration before treatment, and protocols are all plausible. Our cohort also had more advanced disease and was followed for longer, which may give a more honest picture of how denosumab performs in everyday practice.

In animal models of ischaemic osteonecrosis, RANKL inhibition curbs osteoclast activity, preserves trabecular architecture, and lessens femoral head deformity [6]. Translating that preclinical promise into reliable clinical benefit has proved difficult, and the reason is probably that ONFH is multifactorial: vascular compromise, impaired bone regeneration, mechanical insufficiency, and progressive collapse all play a part. Acting on osteoclasts alone is therefore unlikely to halt progression in many patients.

This study has several limitations. First, its retrospective observational design introduces the possibility of selection and information bias. Second, the absence of a control group limits the ability to determine the true treatment effect of denosumab. Third, the relatively small cohort reduces statistical power and limits generalizability. Fourth, bilateral hips from the same patient were analyzed as individual observations, which may have introduced clustering effects. Fifth, baseline prognostic variables such as ONFH etiology, duration of symptoms, lesion size, lesion location, Kerboul angle, and previous treatment history were not consistently available and therefore could not be analyzed. Finally, the exact timing of conversion to THA was not recorded, precluding survival or time-to-event analysis. These limitations should be considered when interpreting the findings.

5. Conclusion

For all its biological logic and the encouragement of early reports, denosumab did little to change the course of femoral head osteonecrosis in this cohort. Many hips progressed radiologically and went on to total hip arthroplasty, which argues that blocking osteoclast-mediated resorption is not, on its own, enough to prevent collapse. Our data do not support using denosumab routinely as a joint-preserving treatment for ONFH, and they hint that it may fall short of established bisphosphonate therapy. Well-designed randomized trials with long follow-up will be needed before it earns a place in standard treatment algorithms.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

Sanjay Agarwala has contributed to conceptualization, design, data collection, analysis, the decision to publish, and preparation of the manuscript.

Mayank Vijayvargiya has contributed to the conceptualization, design, data col-

lection, analysis, decision to publish, and preparation of the manuscript.

Ethics Approval and Consent to Participate

This retrospective observational study was approved by the Institutional Ethics Committee (Approval No. 1512-24-SA). As the study involved retrospective review of anonymized patient records without any direct patient contact or intervention, the Institutional Ethics Committee waived the requirement for informed consent.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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