ORIGINAL ARTICLE

PREOPERATIVE DENOSUMAB AND FEASIBILITY OF LESS MORBID SURGERY IN CAMPANACCI STAGE 3 GIANT CELL TUMOUR OF BONE

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Background: Giant cell tumour of bone (GCTB) is a rare, locally aggressive benign bone tumour with slight female sex predilection and affecting young adults 20–40 years of age. World health organization (WHO) has recently categorized GCTB as an intermediate malignant tumour. GCTB is known to be driven pathologically via expression of pro-osteoclastic signals by stromal cells. This is mediated precisely via the expression of RANKL by stromal cells acting in an autocrine fashion on RANK receptor-positive osteoclast-like giant cells and their precursors. While the treatment is primarily surgical, we hypothesized that preoperative denosumab therapy facilitates conversion to a less morbid procedure in an aggressive campanacci grade 3 GCTB, otherwise amenable to joint resection and reconstruction/arthrodesis. **Methods:** A prospective, single arm, interventional study was conducted in Orthopaedics and radiation oncology department of combined military hospital (CMH) Rawalpindi. The duration of study was 36 months. Patients were recruited by purposive sampling technique as per inclusion/exclusion criteria. Denosumab was administered as preoperative adjuvant therapy for 3 months. Pain was assessed utilizing Brief Pain Inventory –Short Form (BPI-SF) and functional status was assessed as per Musculoskeletal tumour society score at baseline and 12 weeks after commencement of denosumab therapy. The intent of surgery pre and post denosumab therapy was ascertained. **Results:** Total of 23 patients were a part of this study. Mean pain scores and MSTS scores prior to and after denosumab were statistically significant with *p*-value <0.01. Pre-denusomab, there was inclination towards resection arthroplasty as the treatment procedure (56.5%). After denusomab therapy, intralesional curettage was choice of procedure with intent executed for 78.3% of cases. **Conclusion:** Denosumab has potential role for giant cell tumour of bone, it makes a less morbid surgery technically feasible. However, recurrence needs to be probed in long term follow up studies.

Keywords: Curettage; Denosumab; Giant cell tumour of bone

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INTRODUCTION

Giant cell tumour of bone (GCTB) is a rare[1], locally aggressive benign bone tumour with slight female sex predilection and affecting young adults 20–40 years of age[2]. World health organization (WHO) has recently categorized GCTB as an intermediate malignant tumour.[3] GCTB is known to be driven pathologically via expression of pro-osteoclastic signals by stromal cells. This is mediated precisely via the expression of RANKL by stromal cells acting in an autocrine fashion on RANK receptor-positive osteoclast-like giant cells and their precursors.[4] This RANK-RANKL interaction fosters osteoclastic activity resulting in continuous bone resorption. Worth mentioning is the recent identification of driver gene mutation in histone H3.3 being reported as characteristic of GCTB.[5] The treatment of GCTB is primarily surgical, may it be an intralesional curettage combined with local adjuncts or a re-sectional option (arthrodesis, joint replacements, amputation). Keeping in view the benign nature of GCTB and local recurrence rates reportedly controlled by adjuncts (liquid nitrogen, phenol, argon beam coagulator, and methyl methacrylate), the re-sectional strategy is considered a high morbidity option for the young adult population group. The most common subarticular location of GCTB has always posed a serious challenge to orthopaedics when deciding the procedure of choice with curative intent.

The so far elucidated pathophysiology with the identification of RANK-RANKL interaction[6] has brought into limelight the role of anti-RANKL monoclonal antibody, denosumab[7,8]. Food and drug administration (FDA) approved the utility of denosumab for locally advanced and metastatic/inoperable GCTB[9] which has revolutionized the research perspectives into adopting a multidisciplinary approach. Denosumab inhibits maturation, survival, and proliferation of giant cells responsible for osteoclastic activity. Apart from this

proven histopathological role, Girolami *et al* have explained possible antiangiogenic activity which may be exerted through RANKL dependant pathway.[10] The osteoclast inhibition, osteoblastic differentiation, and suppression of tumour vascularity have formed the basis of pre-operative denosumab therapy for downstaging the lesion. The proven clinical/radiological response by utilizing denosumab preoperatively[11] has forced researchers to evaluate the utility of less morbid surgical options post-denosumab therapy for GCTB.[12,13] Specifically in Campanacci grade 3 lesions, the conversion to a less morbid option in a young patient carries the proposed advantage of improved functional outcome by preservation of the native joint and reserving the option of resection arthroplasty at a later stage with the longevity of the prosthesis as a key factor in mind.

We hypothesize that preoperative denosumab facilitates conversion to a less morbid procedure in an aggressive Campanacci grade 3 GCTB, otherwise amenable to joint resection and reconstruction/arthrodesis. The department is part of a tertiary care teaching hospital; we work in close collaboration with the radiation oncology department for oncological cases in the form of weekly held multidisciplinary team meetings. The rationale of this study is to ascertain the impact of preoperative denosumab in cases of Campanacci stage 3 GCTB in the context of invasiveness of procedure performed and operative parameters. We would like to extrapolate our findings and continue our follow-up of trial with a keen interest in long-term recurrence-free survival in locally aggressive giant cell tumours of bone.

MATERIAL AND METHODS

The study is an open-label, institution-based, prospective, single-arm, interventional study and was carried out in the Orthopaedics department of the combined military hospital Rawalpindi. The hospital is the apex hospital of the military and is a tertiary care teaching hospital serving as a referral centre for north Punjab, part of KPK, Kashmir and Gilgit Baltistan province. The trial commenced in July 2020 after we sought ethical review board approval vide letter no 1312/06/20 dated 27 Jun 2020. This study is conducted in parallel to our ongoing trial of evaluating response to denosumab therapy in Giant cell tumours of bone. All patients of Giant cell tumour Campanacci grade 3, being candidates for definitive surgery were recruited in this trial.

The sample size was calculated as per the WHO sample size calculator. Anticipating that 96%[12] of the population planned for joint resection/prosthesis replacement will undergo less morbid procedure mandates 15 patients. (95% confidence level and 0.10 absolute precision). Patients were recruited by purposive sampling technique.

Inclusion/exclusion criteria: Patients 18 years or older, skeletally mature, histologically proven giant cell tumour of bone campanacci grade 3[11] and radiologically measurable disease on radiograph/CT/ MRI with minimum dimension 10 mm in one view were included in this trial. Exclusion criteria included, campanacci grade 1 or 2 (treated primarily with intralesional surgery without denosumab), histopathologically inconclusive non-GCTB giant cell rich lesion, suspected sarcoma at diagnosis, pregnancy, brown tumour of hyperparathyroidism, Paget's disease, known history of second malignancy in past 5 years and recent radiation to the affected extremity in last one month. Informed consent was seeked from all patients being considered to be recruited.

A thorough evaluation included detailed history including patient name, age, gender, contact info, site of GCTB, location with respect to joint and size of lesion on presentation.

The protocol at our department was to pick cases of GCTB already undergoing denosumab therapy in oncology department. Later on, with evolving evidence and consensus in MDT, we modified to limit to a short course of denosumab therapy (6 doses) for all camapancci grade 3 cases who were amenable to surgery

Patients received denosumab in the form of Inj Xgeva (AMGEN turkey) 120 mg S/C on Day- I, Day-8, Day-15, Day-29, Day 57, Day 85. After prior dental evaluation, patients were advised to take calcium and vitamin D supplements daily throughout the period they were undergoing denosumab therapy. Serum calcium, phosphate, renal functions, complete blood picture and coagulation profile was done at 06 weeks and/or at clinicians' discretion. Radiographs/MRI were evaluated at baseline for size of lesion, thickness of ossified rim around lesion and thickness of subchondral bone in adjacent joint. Largest dimension for size, thickness of rim and subchondral bone were considered.

Pain was assessed utilizing Brief Pain Inventory –Short Form (BPI-SF) at baseline and 12 weeks after commencement of denosumab therapy. Patients rated pain severity on an 11-point scale (0, no pain; 1–4, mild pain; 5–6, moderate pain; 7–10, severe pain).[13] The clinical difference in pain scores was also ascertained on basis of MID (Minimum important difference) for BPI- SF. The MID for BPI-SF as explained in literature is defined as minimum change of 2 points in pain score.[14] Functional status was assessed as per Musculoskeletal tumour society score (MSTS) at baseline and 12 weeks. Originally developed in 1985 and revised in 1993 by Enneking *et*

al,[15] the score is a validated and adapted tool for functional status evaluation for upper and lower extremity and has been widely used in orthopaedic oncology. Radiologically patients were assessed 02 weeks after day 85 of denosumab therapy and it included a radiograph and MRI for evaluation of size of lesion, thickness of ossified rim around lesion and thickness of subchondral bone. Clinical and radiological response was quantified and was compared statistically.

The intent of surgery pre and post-denosumab therapy was decided by 3 orthopaedic surgeons independently in concurrence with the radiation oncologist. The decision was made in the multidisciplinary meeting of ortho-oncology and all handover of patients was ensured through MDT proceedings. Our criteria for choosing between curettage and resection depended on tumour extent, site, and response to denosumab therapy. Patients in whom there was no containing bony shell and large soft tissue mass were chosen for resection. Preoperatively, data collected included type of procedure, gritty ossification curettage(Y/N), filling of the bone defect (Bone graft/ Bone substitute/ PMMA), reinforcement type (screws/ Plate), estimated blood loss(ml) and duration of surgery(minutes). Early Range of motion was ensured after surgery for joints to rehabilitate for the best possible functional outcome.

Patients were followed as per a standardized protocol after surgery for clinical and radiological follow up which included 03 monthly follow-ups for 1 year and subsequently 6 monthly radiological follow-ups. After the recruitment of last subject case, the trial continues with follow-up of patients for long-term functional outcomes and recurrence-free survival. Recurrences, need for additional procedures, and conversion to resection arthroplasty /arthrodesis was documented and reported upon completion of 36 months follow-up which is the cut-off for termination of the current trial.

Data analysis was done utilising Statistical Package for Social Sciences for Mac (SPSS) IBM Corp. Version 24.0; IBM Corp, Armonk, NY). Mean and Standard Deviation for quantitative variables and frequency/percentages were computed for qualitative variables. Paired t test was used to compare mean pain scores and functional outcome (MSTS scores) at presentation and at 12 weeks. Mean thickness of subchondral bone, thickness of ossified rim surrounding lesion and size of residual lesion prior and post denosumab was compared using paired sample T test to ascertain statistically significant radiological response. A *p*-value of less than 0.05 was considered significant. The intent of surgery pre and post denosumab was reported as frequencies. The preoperative parameters were computed as descriptives, (mean and SD for duration of surgery and estimated blood loss and frequencies for type of procedure, filling defect type, reinforcement type, joint penetration and gritty ossification).

RESULTS

Total of 23 patients diagnosed with Campanacci grade 3 giant cell tumours were a part of this study. Mean age of the patients was 34.6 years (S.D 10.07). male patients were 16 (69.6%) and female patients were 7 (30.4 %). In 14 cases (60.9%), distal femur was involved, 6 cases (26.1%) proximal tibia was involved, one case of proximal humerus, one distal radius and one case proximal femur was involved. Two cases presented as fracture whereas 21 cases presented without fracture. Brief pain inventory (BPI) scores and Musculoskeletal tumour society (MSTS) scores were used to assess the severity of pain and functional outcomes in these patients (Table-1). Mean pain scores at presentation and at 12 weeks of denusomab therapy were 5.6±1.29 and 3.8±0.9 respectively, with *p*-value <0.01, showing significant decrease in pain scores following denusomab therapy. MSTS scores, measuring functional outcome and quality of life, were assessed at presentation and at 12 weeks, was found to be 18.13±4.57 and 21.04±3.79 respectively, with *p*-value <0.01, indicating better functional outcome after denosumab therapy. Mean size of residual lesion was calculated to be 67.65±22.94 prior to denusomab and it significantly decreased to 64.09±22.14 after denusomab therapy. (*p*-value 0.01) Mean thickness of ossified rim surrounding lesion prior to denusomab was 1.22±0.599 which increased to 8.45±20.05 post denusomab therapy. Similarly, mean thickness of subchondral bone was calculated to be 1.35±0.65 before starting denusomab and it increased upto 3.19±0.82 after denusomab treatment as shown in Table-1.

Table-1: Clinical and radiological response to denosumab therapy Mean BPI and MSTS scores at presentation and at 12 weeks

	Pre-denusomab	Post denosumab	*p*-value
BPI-SF*	5.69±1.29	3.87±0.19	<0.01
MSTS**	18.13±4.57	21.04±3.79	<0.01
Size of lesion (mm)	67.65±22.94	64.09±22.14	<0.01
Ossified rim (mm)	1.22±0.599	8.45±20.05	0.098
Subchondral bone (mm)	1.35±0.65	3.19±0.82	<0.01

*Basic pain inventory short form ** Musculoskeletal tumour society score

Table-2: Intent of surgery pre and post denusomab

	Intent pre-denusomab	Intent post-denusomab
Resection arthrodesis*	7 (30.4%)	2 (8.7%)
Resection arthroplasty*	13 (56.5%)	3 (13%)
Intralesional curettage*	3 (13%)	18 (78.3%)
*Frequency (percentage)		

The intent of surgery prior to denusomab therapy and intent of surgery after denusomab was calculated as frequency and percentages as shown in table 2. Pre-denusomab there was inclination towards Resection Arthroplasty as the treatment procedure for the lesion. (56.5%) After denusomab therapy, it was computed that Intralesional curettage was choice of procedure with intent of 78.3%. Post denosumab therapy, a total of 15 out of 20 cases (75%) intended for resection arthrodesis/ arthroplasty underwent extended intralesional curettage, with gritty ossification curettage in all and no joint penetration.

Out of 15, 10 cases amenable to resection arthroplasty and 5 cases amenable to resection arthrodesis were made possible to undergo intralesional native joint sparing procedure. In all cases, filling of defect was done with PMMA as the adjuvant of priority in our centre (Figure-1) and reinforcement was done with Osteosynthesis (distal femur and proximal tibia anatomical plates).

Resection arthroplasty was done for 3 cases, 2 cases of distal femur and one case of proximal femur. Two cases of arthrodesis included a knee arthrodesis and a case of proximal humerus resection and arthrodesis. The mean duration of surgery for extended intralesional curettage group was 65.72±1.62 minutes and mean duration for resection arthroplasty was 186.0±10.5 minutes. Estimated blood loss as per gauze count/ weight method was calculated as 125.8±28.9 ml for curettage and 800.0±152.7ml for resection arthroplasty/arthrodesis cases. We have received 3 cases of recurrence (13.04%) so far, two cases of proximal tibia 26- and 33-years age, (first case at 23 months and second case at 27 months post-operative), one 32 years age distal femur (27 months).

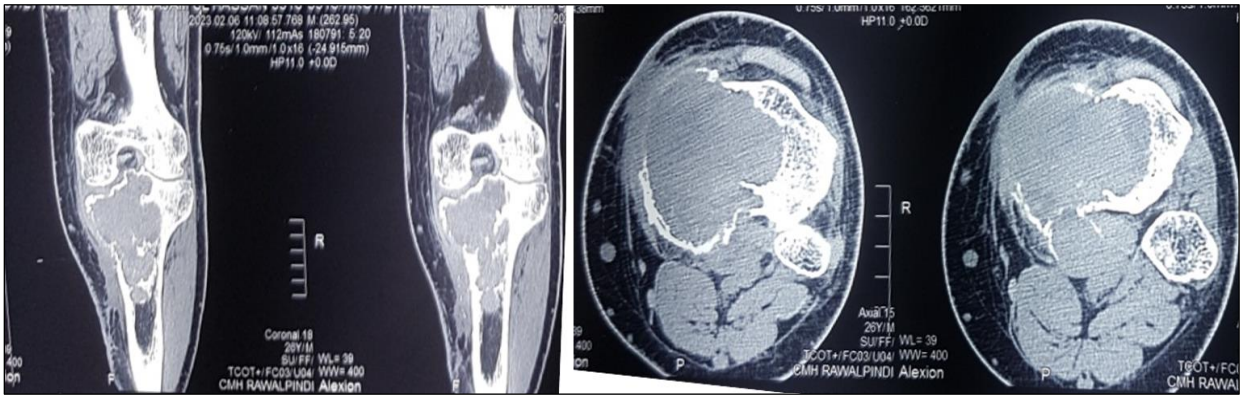
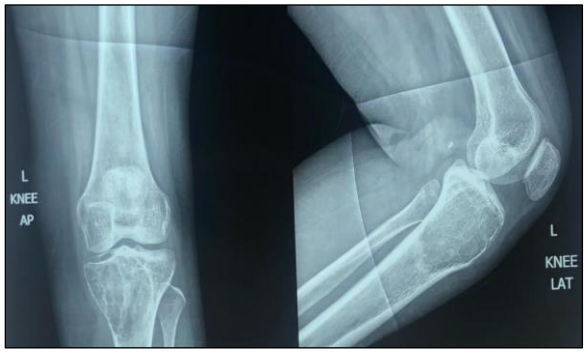
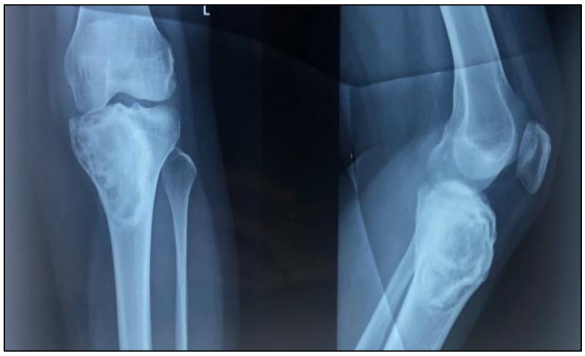


Figure-1: Giant cell tumour of bone (GCTB) medial tibial condyle Left

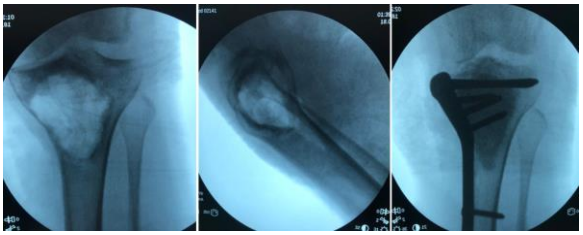
(a) GCTB left medial tibial condyle, radiographs and CT delineating cortical thinning and radiolucent lesion in medial tibial condyle with absent sclerosis and cortical breach with extension in soft tissues.



(b) 08 weeks post denosumab therapy cortical thickness increase and sclerosis visible with formation of subchondral bone



(c) 12 weeks post densumab therapy, lesion appears radiopaque and dense sclerosis and thick subchondral bone with concomitant decrease in pain scores and improved functional outcome of knee joint.



(d) Extended intralesional curettage utilizing Polymethyl methacrylate and reinforcement

DISCUSSION

The treatment of giant cell tumour of bone is primarily surgical. By subjecting patients of campanacci grade 3 to undergo denosumab therapy, we don't advocate denosumab as a primary treatment option for GCTB. We have reported our case series of resectional surgeries for benign GCTB in 2017, whereby mainstay of management for all grade 3 was resection arthroplasty with mega prosthesis or arthrodesis.[18]

Our current trial has small sample size, but we had standardized protocols of denosumab dosage, duration and convenience of timing of surgery. The duration of denosumab for preoperative adjuvant therapy remains debatable till to date. Conventional recommended dose is 6 months duration. Some studies advocate a short duration <3 months which can facilitate curettage and make surgery easy.[19] Studies comparing short and standard duration have proven that short duration has similar clinical and radiological response as that of longer duration and has added benefit of less treatment cost and complications. We have found a significant statistical clinical response in form of decreased BPI- SF with reduction in scores of 1.8±0.30. at 12 weeks of denosumab therapy. Clinical improvement has also been reported in literature by martin broto *et al*[11] and various other authors[20,21]. Our results support the existing role of denosumab therapy and its utility in improving the clinical symptoms.

Two of our patients had fracture, which healed with categorical clinical union after denosumab therapy. Traub *et al* evaluated radiological response in 20 cases after 6 months denosumab therapy, a radiological response was seen in all 20 cases with formation of subchondral bone and rim allowing less morbid surgery in 18 cases. Authors concluded a consistent response with pre-operative denosumab therapy but no reduction in local recurrence was evident.[16] Branstetter also evaluated a favourable radiological response in 20 adults of recurrent and unresectable GCTB.[22] Thomas D assessed radiological and histological response in 37 cases of recurrent and unresectable GCT in an open label phase 2 trial and found no radiological progression of tumour in 10 out of 15 cases after 6 months of denosumab therapy.[8] Denosumab has found to have a RANKL mediated antiangiogenic effect which is observed initially by girolami et al and later in past few years, this effect has been evaluated in literature by utilizing radiology or surgery.[23,24] We have observed this phenomena per-operatively in the form of gritty, bloodless wall of tumour and mean estimated blood loss in intra-lesional surgery was 125.8±28.9 ml.

The feasibility to a less morbid surgery has been probed in literature, Puri published his results for 44 cases of GCTB in which denosumab therapy was given in 22 cases. Results were concluded in doing 21 curettage procedures and 5 conversions from resection to curettage. The authors concluded that a short course can facilitate surgery and make it technically easier.[19] Our results in context of conversion from resection to curettage are quite convincing so far in the form of successful conversions to less invasive procedures after a short course of denosumab.

The debate of local recurrence after combining preoperative therapy with intralesional surgery is a matter of significant concern. The possible harbouring of giant cells in neo-osteoblastic proliferation and continuous stromal cell proliferation despite on denosumab therapy is the postulated cause of recurrence in GCT. This gives a false sense of gritty curettage and avoidance of joint penetration at the cost of leaving behind harboured giant cells. In a retrospective study, overall local recurrence of 47.8% was observed. The group with intralesional curettage without preoperative denosumab had 42.2% (38/90) and in preoperative denosumab therapy prior to curettage had 28.6% recurrence (4/14). Authors emphasized denosumab as a potential therapy but keeping in mind that the recurrence is still frequent.[25] In a therapeutic level 3 study, denosumab was found to be the poor prognostic factor on univariate and multivariate analysis when local recurrence and joint preservation were considered. With joint preservation in 80% of cases, a recurrence rate of 60% was observed in a follow up of 85.6 months.[26] Chinder PS retrospectively reviewed records of 123 patients and divided into those with and without denosumab prior to extended curettage, and found an overall recurrence of 26.8%, with much higher recurrence in denosumab group (42.8 %) as compared to without denosumab group (18.5%). Multivariate analysis revealed use of denosumab as the only factor independently associated with local recurrence following surgery (p=0.002). Patients treated with denosumab had a lower recurrence free survival rate (log-rank, p=0.01).[27] We have so far observed recurrence in 3 / 23 cases (13.04%) in approximate 37 months of follow up, none of our patients has lost to follow up so far. The probable reason can be our meticulous attention towards extended curettage, whereby C-arm guided curettage especially of subchondral bone is done after

creating a large cortical window until pre-treatment rim and margin is reached. We don't want to be advocating a "licence to recur", but we want to ascertain if a low/ acceptable recurrence can give sufficient number of years to preserve the native joint and reserve the resection arthroplasty at a later stage.

The limitations of this study are that it is a single institute-based study, with no control group (without denosumab therapy), a propensity matching of which could have led to meaningful analysis of results. Another limitation is a possible physician discretion bias. We ensured that three orthopaedic surgeons and radiation oncologist independently convey their intent of surgery based on available clinical and radiological response, but a bias could have resulted in favourable figures of less morbid surgery due to physician discretion involvement in determining intent. Our third limitation is inadequate postoperative duration of follow up so far. To ascertain conclusive figures of recurrence, the patients need a longer follow up minimum 48 months or more. We intend to review follow up of our patients at appropriate interval when at least 48 months of last recruited patients are complete.

CONCLUSION

To conclude with, Denosumab has potential role for giant cell tumour of bone, it exerts its action via RANK- RANKL pathway, produces a clinical and radiological significant response and makes a less morbid surgery technically feasible. By giving short term preoperative denosumab therapy for 3 months, resections can be converted to intralesional surgeries, thus preserving the native joint resection arthrodesis/arthroplasty in a young population subset. The risk of recurrence needs to be probed in detail by long term follow up studies. Future studies recruiting more potentially eligible cases of giant cell tumour of bone i.e. unresectable or inoperable, would clarify queries of duration, dosages and safety profile in context of recurrence in mature adults. While the studies are underway, denosumab will remain at forefront for researchers in the management protocol of giant cell tumour of bone.

AUTHORS' CONTRIBUTION

MAR: Conceptualization, design, literature search, data collection, analysis, write-up. MSA: Conceptualization, design, literature input, supervision, data collection. MSN: Data collection, data analysis, interpretation, proofreading. MNC: Data collection, proofreading, study design. AF: Data collection, proofreading.

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