Outcomes of Clinical Trials on Osteonecrosis of the Jaw

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Abstract

Objective: The purpose of this study was to provide a cross-sectional view of all registered clinical trials enrolling patients with osteonecrosis of the jaw (ONJ). The primary aim was to report predictors of trial completion and publication of results.

Materials and Methods: This is a cross-sectional study of ONJ trials registered with ClinicalTrials.gov. For each included entry, trial characteristics and endpoints were recorded. Predictors were enrollment size, etiology, study type, intervention type, sponsor, funding, study locations, number of centers, and specialty of the principal investigator. Outcomes were trial status, publication on PubMed, journal of publication, and length of time between endpoints. Associations between predictors and outcomes were evaluated using chi-square tests and t-tests.

Results: The final sample included 26 trials. Overall, 50% of trials were completed and 69% of completed trials were published. Three out of four terminated trials were suspended due to lack of funding. The median enrollment for completed trials was 149 participants with a mean length of five years. All trials included medication-related osteonecrosis of the jaw (MRONJ) patients and 26% also included osteoradionecrosis of the jaw (ORNJ) patients. The majority of trials were observational (65%), conducted internationally (62%), and involved multiple centers (54%). Published trials had a mean time of 5.9 years between trial start and publication, which was comparable to trial length (p=0.90) and appeared in either dental (44%) or cancer (56%) journals. Completion and publication rates were not significantly increased by industry sponsorship/funding, larger enrollment sizes, or multi-center involvement. Oral and maxillofacial surgery was the most represented dental specialty of principal investigators (56%).

Conclusions: The majority of completed ONJ trials had their results published in a timely manner. Evidence-based investigation of ONJ is a multi-disciplinary and international effort. Among all specialists, oral and maxillofacial surgeons led the most ONJ trials.

Introduction

The goal of evidence-based healthcare is to make clinical decisions based on objective data. Ideally, all clinical decisions would be supported by level I evidence, which requires the presence of at least one randomized controlled trial. Unfortunately, up to half of all randomized controlled trials do not result in a publication. Unpublished research hinders medical advancement. Discoveries should be reported regardless of the results [1], and publication bias may lead to false and inappropriate conclusions [2]. Unpublished or incomplete clinical trials also waste research dollars that could have otherwise been allocated to other more fruitful efforts. Although the randomized controlled trial is the most rigorous form of research, there are many barriers that preclude its success.

Osteonecrosis of the jaws (ONJ) research is relatively young in comparison to other medical diagnoses. ONJ is of great research interest because there are few consensuses regarding its medical and surgical treatment. ONJ has been described in the literature dating back to over a century, and it has a variety of etiologic subtypes such as osteoradionecrosis of the jaw (ORNJ) from radiation. The recent interest in ONJ research was spurred by an increasing number of cases attributed to the use of anti-resorptive medications.

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) was first reported by Marx in 2003 [3], and a variety of well-described risk factors have since been identified [4]. In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) renamed BRONJ as medication-related osteonecrosis of the jaw (MRONJ) in order to respect the role of other medications (e.g., receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitors, anti-angiogenic agents, mechanistic target of rapamycin (mTOR) inhibitors) in
the disease process [5]. The resurgence of interest in ONJ has led to an increase in the number of literature publications. Clinical trials investigating ONJ are of great importance to oral and maxillofacial surgery (OMS) because many patients with ONJ seek OMS care. The aim of this study is to identify factors associated with the successful completion and/or publication of ONJ trials.

**Materials And Methods**

A cross-sectional study was conducted using ClinicalTrials.gov, a publicly available clinical trial registry run by the United States (US) National Library of Medicine at the National Institutes of Health (NIH) [6]. The database was searched for entries containing the key phrases "jaw osteonecrosis," "osteonecrosis of jaw," and "osteonecrosis of the jaw". The National Clinical Trial (NCT) number and trial characteristics were recorded.

Predictor variables included actual or estimated enrollment size, etiology (MRONJ or ORNJ), study type (observational or interventional), intervention type (drug, procedure, or biological) for interventional studies, trial sponsor (industry, research institute, university, or medical center), source of funding (industry, NIH, or other), location of the trial (US or international), number of centers (single or multi-center), the specialty of the principal investigator (oral and maxillofacial surgery, pharmacology, otolaryngology, oral pathology, etc.), trial start date, and trial completion date if applicable. Outcome variables were trial status (recruiting, completed, withdrawn, or unknown), and for completed trials, trial length, publication of results on PubMed (yes or no), journal of publication, publication date, and publication length (time between the start of the trial and the publication of results).

For trials with a status of "unknown" or "withdrawn", the designated contact or principal investigator was emailed to ascertain the reasons behind the status. For completed trials, PubMed was queried with the principal investigator's name and the keyword "osteonecrosis". Putative articles were searched for the NCT number in the methods section to confirm association with the trial. When publication on PubMed could not be identified, the trial contact or principal investigator were emailed to inquire about the status of results publication.

Descriptive statistics were calculated for all study variables. Associations between predictor and outcome variables were determined using chi-square tests, Fisher’s exact tests, and independent- or paired-samples t-tests. A p < 0.05 was considered statistically significant. Effect sizes were reported as odds ratio (OR) for categorical variables. Data were reported as mean ± standard deviation. Analyses were performed using Statistical Analysis System (SAS) software, Version 9.4 (released 2013, SAS Institute Inc., Cary, North Carolina) and IBM SPSS Statistics for Windows, Version 26.0 (released 2019, IBM, Armonk, New York). As per New York University Langone Health policy, research involving the analysis of de-identified data from publicly available datasets does not require institutional research board approval.

**Results**

The final sample included 26 clinical trials pertaining to osteonecrosis of the jaw (Table 1). At the time of this study, 13 (50%) trials were completed while seven (27%) were still recruiting. Of the three trials with unknown status on ClinicalTrials.gov, two were clarified by principal investigators as withdrawn due to lack of funding (NCT02138554, NCT02566681) and one as still active (NCT02198001). One trial (NCT0209540) was withdrawn due to a lack of funding and enrollment. Actual enrollments ranged from 0 to 572,606 with a median of 149 participants. Estimated enrollments for incomplete trials ranged from 10 to 490 with a median of 120 participants. Actual and estimated enrollment sizes were not significantly different (p = 0.40).

All trials included MRONJ patients (26; 100%); 16 (62%) trials only included BRONJ patients and six (23%) trials also included ORNJ patients. Nine (35%) trials included denosumab and nine (35%) trials included anti-angiogenic agents as etiologies.
| ID            | Status      | Estimated/Actual | Type         | Phase     | Intervention/Study Uln                     | Medical/Industry/Other/International/Other
|---------------|-------------|------------------|--------------|----------|--------------------------------------------|-------------------------------------------------|
| NCT01967160   | Completed   | 2560 (Actual)    | Observational| N/A      | Medical Center, Industry                  | Industry, International Multi Pharmacology        |
| NCT01325142   | Completed   | 271 (Actual)     | Observational| N/A      | Medical Center, University                | NIH, Other US Multi Breast Cancer                 |
| NCT01201330   | Completed   | 572,606 (Actual) | Observational| N/A      | Medical Center, Research Institute        | NIH, Other US Multi Oral Health                  |
| NCT03418454   | Recruiting  | 150 (Estimated)  | Observational| N/A      | Medical Center                            | Other International Single Oral Pathology         |
| NCT02198001   | Unknown     | 100 (Estimated)  | Intervention  | Biological: platelet rich fibrin          | University                                      | Other International Single OMS                   |
| NCT02218554   | Unknown     | 150 (Estimated)  | Intervention  | Procedure: genetic assay                  | Industry                                        | Industry International Single Oral Medicine      |
| NCT02069340   | Withdrawn   | 0 (Actual)       | Intervention  | Drug: zoledronic acid                     | Research Institute, University                   | NIH, Other US Multi Oral Pathology                |
| NCT03390777   | Not yet recruiting | 150 (Estimated) | Intervention  | Biological: plasma rich growth factors    | University                                      | Other International Multi OMS                    |
| NCT00858585   | Completed   | 149 (Actual)     | Observational| N/A      | Medical Center, University                | Other US Single Breast Cancer                     |
| NCT01988607   | Completed   | 484 (Actual)     | Observational| N/A      | Industry                                   | Industry International Multi Pharmacology        |
| NCT00874211   | Completed   | 3571 (Actual)    | Observational| N/A      | Industry, Medical Center, Research Institute | Industry, NIH, Other International Multi Breast Cancer |
| NCT00601068   | Completed   | 35 (Actual)      | Observational| N/A      | Industry, University                       | Industry, Other US Single Oral Pathology          |
| NCT01875458   | Recruiting  | 500 (Estimated)  | Observational| N/A      | University                                 | Other US Single OMS                                |
| NCT04012320   | Completed   | 99 (Actual)      | Observational| N/A      | Medical Center                            | Other International Single Pediatrics            |
| NCT00462098   | Completed   | 54 (Actual)      | Intervention  | Drug: hyperbaric oxygen                   | University                                      | Other US Single Anesthesiology                    |
| NCT02566681   | Unknown     | 10 (Estimated)   | Intervention  | Biological: marrow stem cell construct    | Medical Center, Research Institute               | Industry, International Single OMS               |
| NCT04257721   | Recruiting  | 120 (Estimated)  | Observational| N/A      | Medical Center                            | Other International Multi OMS                    |
| NCT03269214   | Completed   | 20 (Actual)      | Intervention  | Drug: topical phenytoin                   | University                                      | Other International Single OMS                   |
| NCT00592982   | Completed   | 25 (Actual)      | Observational| N/A      | University                                 | Other US Single ENT                               |

Drug:
There were 17 (65%) observational studies and the remaining nine (35%) were interventional. Observational studies were not more likely to be completed than interventional studies \( (p = 0.22) \). The most common intervention was the treatment of osteonecrosis with a drug (56%). Trials were sponsored by medical centers (13; 50%), industry (7; 27%), research institutes (6; 23%), or universities (11; 42%). Funding was provided by the NIH (5; 19%), industry (8; 31%), or another source (22; 85%). Trial completion rates were higher with sponsorship from industries (71% vs. 42%), medical centers (54% vs. 46%), and universities (55% vs. 47%), as well as with funding from industry (63% vs. 44%) and the NIH (80% vs. 43%). The majority of trials had locations outside the US (16; 62%) and involved multiple centers (14; 54%). The specialty of the principal investigator was usually in a dental-related field (16; 62%), with oral and maxillofacial surgery most highly represented (9; 35%).

Characteristics of the 13 completed trials were investigated (Table 2). The mean trial length was 5.0 ± 3.3 years. Intervventional trials were not longer than observational trials \( (p = 0.43) \), and multi-center trials were not longer than single-center trials \( (p = 0.64) \). Nine (69%) trials were published on PubMed with a mean time of 5.9 ± 2.5 years between trial start and publication. Publication length was not significantly longer than trial length \( (p = 0.90) \), and larger enrollments did not increase publication likelihood \( (p = 0.52) \). Published studies had a trial length of 5.8 ± 3.5 years whereas unpublished studies had a trial length of 3.1 ± 2.0 years \( (p = 0.19) \). Publication rates were higher for single-center trials (86% vs. 50%, OR = 6.0) and for trials with industry sponsorship/funding (80% vs. 63%, OR = 2.4) or research institute sponsorship (100% vs. 60%, OR = 2.0) (Table 3). Publications were either in cancer journals (5; 56%) or dental journals (4; 44%).
| NCT Number   | Start Date | Completion Date | Trial Length (years) | Publication on PubMed | Journal                | Publication Date | Publication Length (years) |
|--------------|------------|-----------------|----------------------|-----------------------|------------------------|------------------|---------------------------|
| NCT01130389  | 1/1/07     | 9/1/08          | 1.67                 | Yes [7]               | J Dent Res             | 2/11/11         | 4.11                      |
| NCT01967160  | 1/2/12     | 8/5/19          | 7.59                 | Yes [8]               | Support Care Cancer    | 12/23/17        | 5.98                      |
| NCT01325142  | 8/1/10     | 11/1/14         | 4.25                 | No                    | N/A                    | N/A             | N/A                       |
| NCT01201330  | 1/1/07     | 5/1/08          | 1.33                 | Yes [9]               | J Dent Res             | 2/11/11         | 4.11                      |
| NCT00858585  | 3/1/09     | 9/1/16          | 7.50                 | Yes [10]              | Mol Oncol              | 7/29/15         | 6.41                      |
| NCT01988607  | 2/4/13     | 5/15/15         | 2.28                 | Yes [11]              | Support Care Cancer    | 6/18/14         | 1.37                      |
| NCT00874211  | 12/1/08    | 6/1/19          | 10.50                | Yes [12]              | Support Care Cancer    | 12/7/16         | 8.02                      |
| NCT00601068  | 12/1/07    | 7/1/11          | 3.58                 | No                    | N/A                    | N/A             | N/A                       |
| NCT04012320  | 10/31/18   | 12/31/18        | 0.17                 | No                    | N/A                    | N/A             | N/A                       |
| NCT00462098  | 8/1/06     | 12/1/10         | 4.33                 | Yes [13]              | J Oral Maxillofac Surg | 6/12/12        | 5.86                      |
| NCT03269214  | 9/1/12     | 3/30/17         | 4.58                 | No                    | N/A                    | N/A             | N/A                       |
| NCT00592982  | 10/1/06    | 8/1/13          | 6.83                 | Yes [14]              | J Oral Maxillofac Surg | 9/25/13        | 6.98                      |
| NCT00434447  | 12/1/06    | 2/27/17         | 10.24                | Yes [15]              | Eur J Cancer Care      | 1/30/17         | 10.16                     |

**TABLE 2: Characteristics of completed clinical trials on osteonecrosis of the jaw**

Data sourced from ClinicalTrials.Gov [6].

NCT: National Clinical Trial; N/A: not applicable
### TABLE 3: Predictors of clinical trial completion and publication

NIH: National Institutes of Health

|                          | Completion | Publication |
|--------------------------|------------|-------------|
| **Study Type**           |            |             |
| Interventional           | 33.3%      | 66.7%       |
| Observational            | 58.8%      | 70.0%       |
| **Industry Sponsor**     |            |             |
| Yes                      | 71.4%      | 80.0%       |
| No                       | 42.1%      | 62.5%       |
| **Medical Center Sponsor** |          |             |
| Yes                      | 53.8%      | 71.4%       |
| No                       | 46.2%      | 66.7%       |
| **Research Institute Sponsor** |        |             |
| Yes                      | 50.0%      | 100.0%      |
| No                       | 50.0%      | 60.0%       |
| **University Sponsor**   |            |             |
| Yes                      | 54.5%      | 50.0%       |
| No                       | 46.7%      | 85.7%       |
| **Industry Funding**     |            |             |
| Yes                      | 62.5%      | 80.0%       |
| No                       | 44.4%      | 62.5%       |
| **NIH Funding**          |            |             |
| Yes                      | 80.0%      | 75.0%       |
| No                       | 42.9%      | 66.7%       |
| **Location**             |            |             |
| National                 | 70.0%      | 71.4%       |
| International            | 37.5%      | 66.7%       |
| **Center**               |            |             |
| Single                   | 50.0%      | 85.7%       |
| Multi                    | 50.0%      | 50.0%       |

### Discussion

The 26 clinical trials on osteonecrosis of the jaw had a completion rate of 50%. All three withdrawn trials experienced a lack of funding. This reflects the high financial demand of running a clinical trial and the importance of solidifying a funding source before initiation [16]. Completed trials had a reasonable publication rate of 69% with one trial under review by a journal. This proportion was higher than the 46% [17], 48% [18], and 54% [19] publication rates of ClinicalTrials.gov trials in other areas of research. Results were published without significant delay because the lengths of time to trial completion and publication were comparable. Although trials securing industry funding and sponsorship had a higher likelihood of completion and publication, the boost was not significant and was consistent with other studies [17,19]. Completion and publication rates did not positively correlate with enrollment size or the number of participating centers. Therefore, investigators with smaller teams or limited connections should not be...
Clinical trials on ONJ were largely supervised by investigators in a dental-related field (62%) followed by pharmacology (15%). Oral and maxillofacial surgery was the most represented dental specialty (56%), perhaps owing to surgical treatment of ONJ primarily by oral and maxillofacial surgeons. Pharmacology was likely represented due to the clinical significance of MRONJ.

Publications were limited to cancer and dental journals. Cancer publications were prevalent, and this is unsurprising due to the comorbidities of many MRONJ patients treated with osteoclast inhibitor therapy [8]. One publication in the Journal of Dental Research on the risk factors of bisphosphonate-related ONJ was the 58th most-cited publication on MRONJ [8,20]. All trials included MRONJ patients, but less than one-fourth included ORNJ patients. MRONJ was only recently described by Marx [3], and this research focus likely reflects the perceived novelty of MRONJ relative to other forms of ONJ.

There were several limitations to this study. We were only able to identify a limited number of registered trials and this reduced our statistical power. It should be noted that not all trials need to be registered on ClinicalTrials.gov, such as international ones without US subjects, further reducing the sample size. Future studies should revisit ClinicalTrials.gov to monitor the progress of ongoing studies and see how the registry responds to the discovery of new therapies.

Conclusions
In conclusion, the majority of completed ONJ trials had their results published in a timely manner. Terminated trials cited a lack of funding or enrollment. Completion and publication rates were higher for trials with industry, medical center, and research institute sponsorship and for those with industry and NIH funding. MRONJ as an etiology was more widely studied than ORNJ, and all trials included BRONJ. Evidence-based clinical investigation of ONJ is a highly multi-disciplinary and international effort, calling forth the world’s experts in oral and maxillofacial surgery, pharmacology, oncology, otolaryngology, oral pathology, prosthodontics, and more.

Additional Information
Disclosures
Human subjects: All authors have confirmed that this study did not involve human participants or tissue.
Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.
Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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