THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Minocycline for Reduction of Symptom Burden after Surgery in Patients With Head and Neck Malignancy: A Randomized Study
2013-0510

Core Protocol Information

Short Title	Minocycline for postsurgical symptom reduction in head and neck cancer
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Which Committee will review this protocol?

◉ The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1 Primary Objective

The primary objective of this protocol is to test the efficacy of minocycline in reducing multiple patient-reported symptoms in patients who are undergoing surgery for head and neck cancer.

1.2 Secondary Objectives

Part 1: A secondary objective of this protocol will be to explore predictors of symptom recovery and whether these predictors are influenced by a minocycline intervention.

Part 2: Additionally, we will examine whether the longitudinal pattern of local (saliva) and systemic (plasma) release of damage-associated molecular patterns (DAMPs) and subsequent inflammatory responses during cancer treatment may represent biomarkers of the underlying mechanism of symptom burden.

2.0 Rationale

The study aims to test a symptom-reduction strategy based on underlying symptom mechanisms associated with cancer treatments. Using a double-blinded, randomized placebo-controlled trial, we will evaluate the ability of **minocycline** to reduce the post-surgery symptom burden in patients who have undergone surgery for head and neck malignancy. The significance of this research is that it (a) evaluates a low-toxicity, low-cost symptom therapy, (b) evaluates a therapy that could reduce multiple symptoms that are commonly reported after surgery for head and neck malignancy, and (c) seeks to establish a simple medical symptom-prevention therapy for a disease site and treatment for which the symptom burden is high and few medical symptom-prevention strategies exist.

The central hypothesis to be tested is that the tissue damage induced by surgery will lead to cellular stress and cell death that in turn leads to the release of damage-associated molecular patterns (DAMPs) and other cell-death molecules such as high-mobility group box 1 (HMGB1), S100 calcium-binding proteins A13–A16, nucleosomes, and mitochondrial DNA. It is known that DAMPs skew the immune system to a proinflammatory phenotype that is at the origin of symptom development (Li et al, 2013). The existing evidence from clinical and preclinical studies indicates that an imbalance in proinflammatory versus anti-inflammatory activity contributes to the development of systemic symptoms such as fatigue, pain, and disturbed mood (Dantzer et al, 2008).

The agent to be tested in this trial is minocycline. Minocycline has broad anti-inflammatory and antioxidant properties, even though it is most often used as a synthetic antibiotic tetracycline (Mishra & Basu, 2008). Minocycline has a wide range of anti-inflammatory activity in the brain and peripheral nervous system, which it accomplishes by inhibiting microglial activation through inhibition of the inflammatory pathway (Henry et al., 2008).Through systemic administration, minocycline has been proposed to treat rheumatoid arthritis and inflammatory bowel disease, although it is less effective than cytokine antagonists. Because of its lipophilic properties (Aronson, 1980), minocycline also readily crosses the blood-brain barrier, possibly reducing inflammation in the central nervous system and therefore potentially reducing multiple symptom expression at the brain level. It potently downregulates activated microglia, the inflammatory products of which are at the origin of symptoms. The anti-inflammatory effects of minocycline and other tetracycline derivatives may include PARP-1 inhibition (Alano et al., 2006). Among other consequences, minocycline-induced inhibition of PARP-1 may contribute to the inhibition of p38 MAPK activation that has been observed in microglia exposed to minocycline (Tikka et al., 2001; Sapadin & Fleischmajer, 2006). In the context of our current studies on the pivotal role of inflammation in cancer-related symptoms, the downregulation of inflammatory signaling pathways by minocycline is the primary reason for selecting this drug for symptom-prevention clinical trials.
The target of action for the proposed intervention is reduction of proinflammatory cytokines, specifically interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha, likely mediators of multiple symptom expression. Preclinical data suggest that minocycline reduces neural inflammation and prevents apoptosis of neural cells. Animal studies have demonstrated that minocycline reduces the levels of the proinflammatory cytokines IL-6, TNF-alpha, IL-1beta, and interferon-gamma (Ledeboer et al., 2005; Zanjani et al., 2006). This effect, along with the inhibition of microglial activation due to the damaged nerves, has been shown to have neuroprotective action in animal models of a number of diseases, including stroke, multiple sclerosis, and Parkinson's disease, with the potential to be used in preventing and reducing chemotherapy-induced neuropathic pain (Raghavendra et al., 2003). Minocycline's anti-inflammatory effect prevented subacute pathological change in lungs due to inflammation produced by peripheral lipopolysaccharide administration (Yamaki et al., 1998). It effectively modulated mechanical hyperalgesia in newly developed animal models and prevented loss of intraepidermal nerve-fiber density in oxaliplatin-treated rats (Boyette-Davis & Dougherty, 2011). In a rat model of neuropathy, minocycline affected the development of hypersensitivity (Raghavendra et al., 2003). In addition, minocycline reduces activation of caspases including caspase-1 and caspase-3 which may further limit neural cell death (Stirling et al., 2005). It has been shown to modulate LPS-induced cytokine and chemokine production by inhibiting LPS-induced IKK-alpha/beta phosphorylation (Tai et al, 2013).

3.0 Background

Many cancer patients receive aggressive therapy and experience multiple symptoms that cause them significant distress and impair function and rehabilitation. Whereas many of these symptoms are the result of disease, it is increasingly recognized that pain, fatigue, sleep disturbance, cognitive dysfunction, and affective symptoms can also be caused by cancer treatment (von Gruenigen et al, 2006). Treatment-related symptoms can directly affect survival if they become so severe that patients abandon potentially curative therapies (Borden & Parkinson, 1998; Jeremic et al, 2003). Moreover, treatment-related symptoms may persist for weeks, months, or years and they may worsen even if the cancer improves.

There is growing awareness that common biological mechanisms may cause or contribute to some of these clusters of symptoms at the same time (Barsevick, 2007; Kim et al, 2012; Wang et al, 2006). The theoretical underpinning for the proposed studies, based on the animal model of inflammation-induced sickness behavior, is that dysregulated inflammation and its downstream toxic effects represent a significant biological basis for subjectively reported clusters of symptoms (Cleeland et al, 2003; Lee et al, 2004). Accordingly, optimal symptomatic control would utilize symptom-focused therapies to attack both underlying symptom mechanisms as well as the end effects of these mechanisms.

We have reviewed the evidence of the impact of inflammation on several cancer-related symptoms (Lee et al, 2004). The insult of tumor-reductive surgery increases production of inflammatory cytokines, especially IL-6 and TNF (Bower et al, 2011; Fiorelli et al, 2012; Kim et al, 2011). The inflammatory reaction is a classic feature of surgical trauma and can serve as a prime candidate for the mechanism behind increases in postsurgical symptoms. It has been suggested that reduction of this treatment-induced inflammatory response might significantly reduce the symptoms associated with surgery (Fiorelli et al, 2012).

DAMPs such as HMGB1 and S100 are released locally and in the circulation due to tumor cell death and damage to healthy tissue such as that caused by surgery, as well as actively secreted by activated monocytes or dendritic cells (Lambros et al, 2011; Yang et al, 2013). DAMPs are endogenous danger molecules that elicit inflammation and subsequent immune responses once released from dead or stressed cells (Li et al, 2013). DAMPs may represent biomarkers for symptom development (Chavan et al, 2012; Feldman et al, 2012).

3.1 Symptom Management

The control or prevention of cancer-related cytokine dysregulation presents new opportunities for symptom reduction or prevention. Inflammation can be modulated by a variety of existing pharmaceutical approaches. Thus, a goal of the proposed study is the development of a symptom-management strategy based on underlying symptom mechanisms in combination with empiric treatments.

Better symptom management, in cancer as well as in other diseases, has been hampered by the lack of a strong clinical-trial evidence base for guiding symptom management practice. Several barriers have hindered the development of clinical trials in symptom management. First, the subjective nature of symptoms has limited innovative research into the mechanisms underlying these symptoms and the development of novel ways of treating or preventing them. Special difficulties include the poor fit of current disease models of research for implementing this kind of health-related investigation, along with lack of statistical models that integrate “rough” self-report data and biological data (Cleeland, 2001a). Even so, patient-reported outcomes research has recently been promoted by the U.S. Food and Drug Administration (FDA) for more accurate therapeutic agent evaluation, and symptom reduction has been recognized as a primary clinical benefit for drug approval (US Food & Drug Administration, 2009).

Other barriers have also hindered the development of evidence-based methods for controlling treatment-related symptom burden, despite the availability of more adequate symptom measurement methods. Many of the agents that might be effective in the control of treatment-related symptom burden are generic or off-patent drugs that will never receive clinical research support from the pharmaceutical industry because there is no financial incentive to support testing their effectiveness for symptom control in clinical trials.

Finally, current practice utilizes randomized clinical trials to manage a single symptom with a single agent—for example, pain controlled with a single analgesic. When clinicians do treat multiple symptoms, they typically prescribe multiple agents based on anecdotal experience or the patient’s perceived needs, rather than on evidence-based research (Cleeland, 2001b).

3.2 Head and Neck Treatment Side Effects

Common symptoms of head and neck malignancy and its treatment can significantly impair patients' daily functioning and quality of life. Symptoms such as pain, sleep disturbances, dry mouth, difficulty swallowing, and fatigue add to the burden of head and neck cancer. Patients with serious illnesses often report that they would like to “return to a normal life” (Townsend et al, 2006). Tumor-reductive surgery followed by chemoradiotherapy is the primary treatment for the vast majority of patients. Thus, a goal of the proposed study is to develop a symptom management strategy to improve patient outcomes during the period of survivorship, broadly defined as the clinical course of an individual from the time of diagnosis forward.

4.0 Background Drug Information

4.1 Minocycline hydrochloride (Minocin®, manufactured by Triax Pharmaceuticals, LLC, Cranford, NJ; see Appendix C) is a semisynthetic antibiotic derived from tetracycline. It has the unusual side effect of markedly suppressing proinflammatory cytokine release, which is the primary reason we have chosen this drug as for the intervention arm in this study.

Minocycline has been used safely in thousands of patients over many years to treat a variety of clinical indications. It has a very low toxicity in preclinical studies and a sufficient safety profile as demonstrated in many studies of long-term use in humans. Minocycline was suspected in less than 2.5% of all common adverse events reported to the FDA (http://www.drugcite.com/?q=minocycline).

The therapeutic effects of minocycline have been investigated in a number of pathological domains, including dermatological and autoimmune disorders (Sapadin & Fleischmajer, 2006). Minocycline’s long-lasting effects in preventing neuropathic pain (Padi & Kulkarni, 2008; Raghavendra et al., 2003) and as a potential remedy for human inflammatory bowel disease (Huang et al., 2009), neurodegenerative disorders (Noble et al., 2009), and HIV (Zink et al., 2005) have been reported. Minocycline was safe and effective for patients with rheumatoid arthritis in a 48-week double-blind placebo-controlled trial (Tilley et al., 1995). Recent clinical trials for Fragile X Syndrome (Paribello et al., 2010), vitiligo (Parsad & Kanwar, 2010), and schizophrenia, in which minocycline was used to block nitric oxide-induced neurotoxicity (Levkovitz et al., 2010), have shown a significant benefit from this well-tolerated agent. Minocycline was found to decrease levels of IL-6 and the acute-phase response protein C-reactive protein (CRP) in patients with rheumatoid arthritis (Kloppenburg et al., 1996), and it is now widely used in the management of dermatitis associated with targeted therapy in cancer. A recent exploratory study of retrospective clinical data showed that minocycline reduced the frequency of reporting severe pain after third-molar surgery (Gelesko et al, 2011).

Commonly associated side effects of minocycline include light-headedness, vestibular symptoms, headache, and nausea (Gump et al, 1977), with no correlation seen between serum concentration and toxicity (Kloppenburg et al, 1995). In community patients with rheumatoid arthritis (RA), side effects of long-term minocycline treatment (> 10 years) included skin effects (54%), dizziness (9.5%), and nausea (5.1%) (Smith et al, 2011). Hyperpigmentation, the most common skin side effect, has been reported in treatment of acne vulgaris, acne rosacea, autoimmune bullous disease, and RA (Ozog et al, 2000). The median elapsed time to the development of minocycline-induced hyperpigmentation in patients with RA was 9.1 months (range 2.2–77.8 months) (Fay et al, 2008).

4.2 Absolute Contraindications to Study the Symptom Intervention Agent Minocycline

4.21 Hypersensitivity to any tetracycline.
4.22 Pregnancy.
4.23 Hepatotoxicity: Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal.

4.3 Minocycline Common Adverse Reactions

Minocycline: Dizziness (9%) and vertigo.

4.4 Minocycline Monitoring Parameters

4.41 Minocycline: LFTs, BUN, serum creatinine

4.42 Signs of acute hepatitis: rash, fever, malaise, abdominal pain, and vomiting. [Evidence: Hepatotoxicity (e.g., elevated hepatic enzymes, hyperbilirubinemia, hepatic cholestasis, hepatic failure with some fatalities, hepatitis with autoimmune features, and jaundice) have also been reported. Abdominal complaints may suggest hepatotoxicity; the incidence of this effect is roughly 4.7%. Liver toxicity is possible with excessive accumulation of the drug, which can occur in patients with renal impairment receiving even usual oral or parenteral doses.

4.5 Minocycline Drug Interactions

4.51 Antacids containing calcium, magnesium, or aluminum, bile acid sequestrants, bismuth, oral contraceptives, iron, zinc, sodium bicarbonate, penicillins, quinapril may decrease absorption of minocycline. Avoid taking these substances within 2 hours of using this medication.

4.52 Methoxyflurane anesthesia, when concurrent with minocycline, may cause fatal nephrotoxicity.

4.53 Vitamin A or related compounds (i.e., retinoids), when taken concurrent with minocycline, may increase the risk of benign intracranial hypertension.

4.54 Minocycline may enhance the action of oral anticoagulants (warfarin, anisindione). International normalized ratio (INR) should be monitored whenever a tetracycline is started or stopped, and the patient should be observed for signs of bleeding. Patients should be advised to notify their physician if they experience any signs of excessive anticoagulation, such as unusual or prolonged bleeding, bruising, vomiting, change in stool or urine color, headache, dizziness, or weakness.

4.6 Serious adverse events for minocycline

No serious adverse events (SAEs) have been attributed to this trial agent.

4.7 Storage Information

4.71 Capsules: Store at 20°C to 25°C (68°F to 77°F); protect from heat, light, and moisture.

4.72 Injection: Store vials at 20°C to 25°C (68°F to 77°F) prior to reconstitution. Reconstituted solution is stable at room temperature for 24 hours. Final dilutions should be administered immediately.

5.0 Study Design

Using a double-blinded, randomized placebo-controlled trial, we will evaluate minocycline's ability to reduce the symptom burden after tumor-reduction surgery in patients with head and neck cancer. Blinding is especially important in trials where symptom reduction is the outcome and where knowledge of the treatment arm might bias assessment staff or patients. The compounding pharmacy will prepare the appropriate active agent and placebo for each patient.

Design: Phase II, 2-arm, double-blinded, randomized placebo-controlled trial

Symptom Intervention Agent: minocycline or placebo, 100 mg twice a day

Intervention Period: 22-23 days: Intervention agent daily from not more than 2 days and not less than 1 day before surgery to the end of 3 weeks after surgery, for a total of 3 weeks plus 1-2 days.
Primary Outcome Variable: 3-week (+/– 7 days) area under the curve (AUC) using the average of 3 symptoms (pain, fatigue, and disturbed sleep) measured with the M. D. Anderson Symptom Inventory head and neck cancer module (MDASI-HN). The MDASI-HN will be administered before, during, and after surgery. Please see Section 10 for the assessment schedule.

A total of 130 patients will be randomized to either minocycline or placebo, 65 in each arm. AUC values for patients who drop out of the study after providing a week of AUC data will be included by carrying their last symptom data forward for the remaining study period under the intent-to-treat rule. The carryforward method of handling dropouts will be revisited upon completion of the study to determine if adjustments to these values can be made using longitudinal regression models estimated from patients who completed the entire study. All grade 3 and 4 toxicities reported by patients in this trial will be evaluated by the treating physician in consultation with the Principal Investigator, or other attending physician if the Principal Investigator is not available, to determine if the toxicities were caused by the study medication rather than the surgery. We will use standard 3+3 criteria for determining whether treatment exceeds either grade 3 or 4 toxicities for the first 6 patients assigned to minocycline. That is, if more than 1 symptom intervention-related toxicity (grade 3 or 4) in the first 6 patients assigned to minocycline is observed, the study will be terminated.

A list of adverse events known to be associated with primary treatment is listed in section 4.0 of the protocol.

The screening for potential drug interactions will be the responsibility of the research staff. The research staff will review the medications the patient is taking prior to initiating treatment and will document any new medications prescribed during the course of the trial. During the trial, the research staff will capture any drug interactions causing an adverse event, according to institutional procedures. Medication information leaflets will be provided to both patients and treating physicians to inform them of the possibility that the patients may be taking minocycline (Appendices W and X). The research staff has conducted many of these studies and has the appropriate skills to perform these tasks.

6.0 Administration of the Pharmacological Agent

As stated in Section 5, preparation and dispensing of the study medication (minocycline or placebo) for each patient will be coordinated by Investigational Pharmacy Services in the Division of Pharmacy at MD Anderson, supported by the Cancer Center Support Grant. The study medication will be compounded at the GreenPark pharmacy, which has done this same minocycline/placebo compounding for several of our other studies. Matching 100-mg capsules containing a matching powder will be compounded for both minocycline and placebo. Patients will pick up the assigned study medications at one of the outpatient pharmacy stations at MD Anderson. At pickup, patients will receive instructions regarding how to take study medications.

The participants will take study medication twice daily, starting not more than 2 days and not less than 1 day before surgery, and continue for 3 weeks postsurgery. The final day of study medication will be the 21st day after surgery.

Patients will begin taking study medication (minocycline or placebo) on Day –2 or Day –1, (i.e., 1 or 2 days prior to surgery), 100 mg given orally every 12 hours. Patients who have a feeding tube may take powdered drug or placebo from the capsule in a diluted form through the tube. At any time that patients are unable to take study medication orally or through their feeding tube, 100 mg of study medication will be administered intravenously every 12 hours. The 100 mg of study medication can be diluted prior to administration with 500 mL IV solution (i.e. normal saline or D5%). The rate of infusion will be 9 cc/minute, for a total infusion time of 60 minutes. Because the IV solution of minocycline is yellow, study medication will be dispensed from an amber bag to prevent accidental unblinding.

The table below displays the symptom intervention agent and the dosing schedule.

Symptom Intervention Agent	**Dosage Forms**	**Dosage**
Minocycline - IV Placebo - IV	100 mg IV (intraoperatively)	100 mg 2 times a day
Minocycline – Oral Matching placebo - Oral	100 mg capsules	100 mg 2 times a day

6.1 Postdischarge Dosing
After discharge, patients will continue taking the study drug or placebo 100 mg twice daily until 3 weeks postsurgery. They will be given medications to take home with them. Patients will be asked to bring their study medication container and any unused medication to every clinic visit.

Unused drugs will be returned to Investigational Pharmacy Services by the study staff for disposal. Once the final capsule count is completed, the capsules will be placed into the MD Anderson biohazard waste system by pharmacy staff.

6.2 Intraoperative and Postoperative Anesthesia Care
In the preoperative holding area, patients will receive intravenous midazolam if clinically indicated according to the anesthesiologist's judgment. Prophylactic antibiotics will be given per surgical routine. Steroids will not be allowed, unless specifically indicated by life-threatening conditions.

General anesthesia will be induced with fentanyl or sufentanil and propofol intravenously according to the anesthesiologist's clinical judgment. Tracheal intubation will be facilitated by succinylcholine or a nondepolarizing muscle relaxant. Anesthesia will be maintained with desflurane or isoflurane in (50%–100%) oxygen or propofol infusion according to the anesthesiologist's clinical judgment. Intraoperative analgesia will be obtained by the intravenous administration of sufentanil. Sufentanil or fentanyl will be administered if pain control is deemed to be insufficient at the time of incision or at any time during the surgery. Alternatively, intravenous boluses of fentanyl or hydromorphone might be given according to the anesthesiologist's clinical judgment. Hemodynamics will be maintained according to the clinical anesthesiologist's judgment. The lungs will be mechanically ventilated to maintain end-tidal PCO2 near 40 mmHg. Normothermia will be maintained with forced-air warming. Antiemetics will be given according to the anesthesiologist's clinical judgment. In those patients deemed to be awakened from general anesthesia when surgery is complete, muscle relaxation will be antagonized and the trachea extubated. At the end of surgery, hydromorphone or fentanyl will be given intravenously if considered necessary for pain control. All patients will receive acetaminophen intravenously 20 minutes before surgery is finished, unless specific contraindications to the drug are noted. Ketamine, ketorolac, or celecoxib will not be administered at any time. In the postoperative care unit, all patients will receive intravenous boluses of fentanyl or hydromorphone for pain control. In those patients for whom sedation and admission to the intensive care unit is necessary, intravenous propofol will be given continuously during transport. In the intensive care unit, sedation will consist of propofol or dexmedetomidine according to the intensive care unit physician's clinical judgment.

On the regular nursing floor, postoperative analgesia will be standard of care for this postsurgical patient population, including but not limited to opioids, anti-inflammatory medications, GABA analogs, steroids, and antiemetics. Usage will be recorded and will be considered in the analyses.

7.0 Data Collection Tools

7.1 Patient-Reported Outcome (PRO) Measurements
Altogether, the PRO measurements will take 15–20 minutes to complete.

7.11 Measure of Symptom Burden (Appendix D)
Symptom data will be collected using the head and neck cancer module of the M. D. Anderson Symptom Inventory (MDASI-HN). The MDASI-HN items pain, fatigue, and disturbed sleep will be used to calculate the symptom burden. Prior studies (unpublished data) have indicated that a significant proportion of patients reported these symptoms to be moderate to severe. The MDASI-HN will be collected face-to-face in the clinic, either on paper-and-pencil forms or using a tablet PC; when the patient is away from the clinic, the MDASI-HN will be collected through a telephone-based, computerized interactive voice response (IVR) system, phone calls by field coordinators, or by regular mail to measure symptom burden over time of the treatment.

The IVR System
An IVR system can greatly facilitate the longitudinal tracking of symptoms in patients. IVR systems are programmed to call patients at home for symptom assessment. The IVR system asks patients to rate each symptom and interference item on the MDASI-HN's 0–10 numerical scales using the keypad of a touchtone telephone.

Participants will be provided with an informational brochure outlining the steps to complete an IVR call (Appendix E). A telephone number will be provided in the event of questions or problems. Patients will also be given a Patient Identification Number (PIN) for access to the system. IVR calls will be scheduled at a time that is convenient for the patient.

Completion or failure of calls will be monitored by the research staff. In the event of missed calls, a notification screen will appear in the IVR system to alert the research staff. The research staff will then contact the patient, check on their status and, if possible, complete the assessment with the patient during the telephone interview. The system will continue calling the patient at the preset schedule.

The IVR symptom and interference data will be available on an MD Anderson intranet site with access limited to authorized project staff only. Patient data will be identified by subject study number.

7.12 Measure of Quality of Life (Appendix F)
The EuroQol (EQ-5D) is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The EQ-5D was originally designed to complement other instruments but is now increasingly used as a standalone measure. The EQ-5D's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems" (level 1), "moderate health problems" (level 2), and "extreme health problems" (level 3). A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Each unique state described by the instrument has an associated 5-digit descriptor ranging from 11111 for perfect health to 33333 for the worst possible state. The resulting descriptive system defines 243 health states. In addition, "unconscious" and "immediate death" are included in the EQ-5D valuation process but are not a part of the descriptive system.

7.13 Measure of Global Quality of Life (Appendix G)
The Global Quality of Life (GQL) is a single item asking patients to rate their quality of life on a 0–10 scale over the past week.

7.14 Tobacco History Form (Appendix I)
The Tobacco History Form is a short questionnaire that asks about smoking history.

7.15 Patient-Reported Assessment Checklist (Appendix K)
The Patient-Reported Asessment Checklist is to be completed and signed by the patient each time that the patient-reported outcome measures above are completed either on paper or tablet PC.

7.2 Other Data to be Collected
Research staff will collect demographic and clinical information from the patient's medical record. Demographic data to be collected may include such items as birth date, marital status, race/ethnicity, education, and employment status. Examples of clinical information that may be collected at one or more timepoints during the study include height and weight, disease information (eg, cancer site/stage, HPV status), treatment information (eg, type of surgery, postsurgical status, current medications), comorbidities, and performance status.

Laboratory values from blood analysis, such as C-reactive protein (CRP), serum chemistry (albumin, calcium, phosphorous, glucose, BUN, creatinine, total bilirubin, and total protein), electrolytes (sodium, potassium, chloride, carbon dioxide, magnesium), and complete blood count (CBC), will be recorded if they are available in the patient medical record from a blood draw performed for clinical purposes.

Note: Liver function tests, renal function tests, INR tests, and urine pregnancy tests are required at baseline. If the liver, renal, or INR tests were not performed within the past 3 months prior to starting treatment with the symptom drug/placebo, they will be drawn for eligibility purposes. The study coordinator will perform the urine pregnancy tests.

8.0 Patient Eligibility

8.1 Inclusion Criteria

8.11 Patients with head and neck cancer who are undergoing either flap or nonflap surgery (limited to parotidectomy, hard palate maxillectomy and glossectomy, mandibulectomy, and any procedure with neck dissection) at MD Anderson Cancer Center.
8.12 Patients > 18 years old.
8.13 Patients who have not undergone surgery in the past 6 months. Patients may have had neoadjuvant chemotherapy prior to surgery.
8.14 Patients must have normal renal function test and no prior renal disease. The screening cut off for serum creatinine is < 1.5 mg/dL.
8.15 Patients must have normal hepatic function test and no prior liver disease:
8.151 The screening results for alanine aminotransferase (ALT) must be < 2 times the upper limit of normal for patients to be eligible.
8.152 The screening results for aspartate aminotransferase (AST), if available, must be < 2 times the upper limit of normal.
8.16 Patients who speak English or Spanish (due to the novel research and its complexity, we are only accruing English-speaking or Spanish-speaking patients to the protocol).
8.17 Patients must be willing and able to review, understand, and provide written consent.
8.18 Patients must be willing to discontinue taking dong quai and/or St. John's wort.

8.2 Exclusion Criteria

8.21 Patients who are taking medications (including minocycline) or have conditions that potentially preclude use of the study medication or intervention as determined by the treating physician.
8.22 Patients who are enrolled in another symptom management trial or receiving active treatment under another clinical trial.
8.23 Patients with a history of clinically significant cutaneous drug reaction, hypersensitivity reaction, anaphylaxis or any other serious adverse reaction to any of the anesthetics or analgesics medications used in the study.
8.24 Patients with hypersensitivity to any tetracycline.
8.25 Patients on vitamin K antagonist (i.e., warfarin).
8.26 Patients taking any tetracycline within the last 15 days.
8.27 Patients who have been on opioid therapy for the last 4 weeks or more.
8.28 Patients with bile duct obstruction.
8.29 Patients who are pregnant.
8.30 Patients with INR > 1.5.
8.31 Patients with autoimmune disease.

9.0 Patient Enrollment and Registration

9.1 Patient Enrollment
Patients will be screened for eligibility and recruited for enrollment in the MD Anderson Head and Neck Center no less than 1day before their surgery.

Research staff will maintain a log of all patients screened, and the reasons that patients do not enter the study will be documented.

Eligible patients who agree to enroll in the study will provide written informed consent/authorization.

Enrolled patients will be registered into the institutional patient data-management system.

9.2 Patient Randomization and Assignment to Treatment Arm
The study will accrue a total of 130 patients, with 65 patients each in the placebo and minocycline groups. Because surgical patients who are also being treated with neoadjuvant therapy are likely to have more symptoms, we will use neoadjuvant therapy as a stratification variable. There will be two separate stratification groups, with and without neoadjuvant therapy. Prior to accruing the first patient, a randomization list using permuted block design will be generated by our biostatistician collaborator from the Department of Biostatistics for all 130 patients, stating the stratification and treatment group to which each patient will be randomized. This list containing the accrual number, the stratification group, and treatment group information will be set up in the Clinical Trial Conduct website by the biostatistician collaborator.

Once a patient is enrolled on the study, the Investigational Pharmacy retrieves the randomized treatment arm information from the Clinical Trial Conduct website. Once a patient is randomized to a treatment arm, Investigational Pharmacy will relay the information to the dispensing Pharmacy. The patient visits the most convenient outpatient pharmacy to pick up the study medication assigned.

Patients will pick up the assigned study medications at one of the outpatient pharmacy stations in MD Anderson. At pickup, patients will receive instruction in how to take study medications, and the study research staff will provide a Minocycline Patient Education Leaflet on how to take the drug and its interactions (Appendix W). Study medication use will be reviewed by study staff.

Study staff will contact patients every week to monitor adherence to study medication and to check for adverse events, during routinely scheduled clinic visits or via telephone calls.

9.3 Biological Markers for Minocycline Efficacy
Blood and saliva will be collected at the times shown in the Assessment Schedule (Section 10.0) to evaluate patients' responses to the intervention. These specimens will be used to determine the local secretion of DAMPs (saliva), serum cytokines, and serum DAMPs (such as HMGB1, nucleosomes, S100 calcium-binding proteins A13–A16, and nucleosomes).

A 10-mL blood sample for serum will be collected. The blood draw will be ordered in accordance with usual MD Anderson processes. Study staff will collect the saliva samples using a salivette (citric acid cotton swab). Saliva (0.5-1.0 mL) will be collected by gently chewing on the cotton swab for 2-3 minutes.

Blood samples will be transferred on ice to the research laboratory immediately after sampling. Saliva samples will be transferred on ice to a research lab immediately after sampling and frozen at –20°C. Samples will be moved batchwise once a week to a –80°C freezer for storage until testing.

10.0 Assessment Schedule

	Baseline[a]	**Day 0 (day of surgery)**	**Day 1[b]**	**Day 3[b]**	**Day 5[b]**	**Day 7[c]**	**Day 10[c]**	**Day 14[c]**	**Day 17[c]**	**End of Intervention (Day 20 ± 7 days)[d]**	**Week 6 ± 1 week post-surgery (in clinic or by phone)[d]**
MDASI-HN	X	X	X	X	X	X	X	X	X	X	X
EuroQol (EQ-5D)	X		X	X						X	X
Global Quality of Life (GQL)	X		X	X						X	X
Tobacco History	X										
Alcohol History	X										
Patient-Reported Assessment Checklist	X	X	X	X	X	X	X	X	X	X	X
Demographic information, disease history, current disease status	X										
Comorbidity information	X										
Surgical summary and current											X[g]

disease status											
Other clinical information[e]	X					X		X		X	X
Laboratory information	X					X[g]				X	X
Medication information	X		X			X				X	X
Study medication accountability		X				X		X		X	
Research blood draw[f]	X		X			X				X	X
Saliva sample[f]	X		X			X				X	X

[a] All baseline assessments will be completed at the time of enrollment. The first dose of study medication will be given 1 or 2 days before surgery.
[b] With a 1-day window and if patients are able (e.g. not intubated or not sedated).
[c] With a 2-day window and if patients are able (e.g. not intubated or not sedated).
[d] End of intervention (last day of study medication) is Day 20 postsurgery; end of study is the clinic visit closest to Day 20. These could coincide, in which case all assessments shown for these two time points will be completed once.
[e] For example, ECOG performance status, height, weight. Laboratory values are recorded when available; monitoring occurs weekly.
[f] Saliva and blood sampling will occur before surgery; at the first postoperative blood draw, whenever it occurs (shown as Day 1 in table); at discharge or Day 7, whichever occurs first; and at the end-of-intervention and end-of-study clinic visits. All blood and saliva sampling will occur if feasible, e.g., patient has other diagnostic blood sampling ordered or is willing to provide sample, patient is in clinic.
[g] Most recent information available.

10.1 Data Confidentiality Plan

Study data will be collected on paper forms or electronically. Completed paper forms will be sent to data management in the Department of Symptom Research for scanning, verification, analysis, and storage in a locked cabinet in the department. Copies of the signed informed consent document will be kept in a secure file in the Department of Symptom Research and are available upon request. All electronic data, including scanned data, is kept on a password-protected MD Anderson secure server.

Study personnel needing access to the electronic or paper files for analysis will have access to secure files by password or key. Files may only be accessed when analysis is occurring and may not be kept by study personnel when not in use. Files will be identified with participant study numbers and initials only and not with names, medical record numbers, or other identifying information. Raw performance data will be recorded under the anonymous identifiers only. Blood samples will be marked using the same anonymous identifiers used for the data and stored at the Neuroimmunology Laboratory.

A custom software application is available for protocol tracking. The software monitors patients as they progress through the protocol from screening to off-study and informs the data coordinators of protocol events and which CRFs to administer.

Study data may be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson. REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies (Harris et al, 2009). REDCap provides: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. REDCap is hosted on a secure server by MD Anderson's Department of Research Information Systems & Technology Services (https://redcap.mdanderson.org). REDCap has undergone a Governance Risk & Compliance Assessment (05/14/14) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and MD Anderson's Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. Users are authenticated against MD Anderson's Active Directory system. External collaborators are given access to projects once approved by the project sponsor. The application is accessed through Secure Socket Layer. All protected health information will be removed from the data when it is exported from REDCap for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number.

After all analysis has been completed and all study results have been reported, the electronic and paper files will be permanently and securely archived. Patient data will be stored in an institutional big data warehouse and made available to all research and clinical faculty, with appropriate validation and access controls, so it can facilitate research cross-fertilization and speed insight discovery.

11.0 Adverse Event Reporting

11.1 Adverse Events (AE)

All patients will be seen by research staff throughout the duration of the hospital stay postsurgery, allowing for close monitoring of potential adverse events by clinical and research staff during treatment.

After discharge from the hospital, patients will be monitored for the remainder of the study through weekly phone calls by the research staff. In addition, patients will be given a contact phone number for treatment-related questions.

Toxicity and other clinical variables will be collected weekly by research staff. Treatment-related toxicities (NCI Common Terminology Criteria for Adverse Events, version 4) will be monitored by both clinical and research staff at the patient's regular clinic appointments (Appendix P).

Grade 1 and Grade 2 AEs will not be reported. AEs that are Grade 3 and above are considered to be serious adverse events (SAEs) and will be reported. SAEs that are **unexpected and related** (definitely, probably, or possibly related) to the study medication will be reported promptly according to institutional policies (see Section 11.2 below). SAEs that are either (1) **expected** or (2) **unexpected but unrelated** (unrelated or unlikely to be related) to the study medication will be summarized on the continuing review report. The principal investigator and the treating physician will determine whether or not an AE is related to the study medication.
The PI or physician designee is responsible for verifying and providing source documentation for all AEs and assigning the attribution for each event for all subjects enrolled on the trial.

If in the course of assessing symptoms, the patient reports a severe symptom (7 or above on the MDASI's 0-10 scale), the data collector will determine if the patient's healthcare provider is aware that the patient is experiencing this severe symptom. If the healthcare provider is not aware, the data collector will determine whether the patient intends to inform the healthcare provider of the symptom and its severity within 24 hours. If the patient does not intend to inform the health care provider, the data collector will inform the patient that the data collector will let the health care provider know of the severity of the symptom within 24 hours. If in the course of assessing symptoms, the data collector becomes aware of any imminently life-threatening condition (e.g., extreme shortness of breath, suicidal ideation) that the patient is experiencing, the data collector will let the patient know that the data collector will be informing a healthcare provider immediately of the condition. The data collector will then immediately initiate contact with a healthcare provider.

11.2 Serious Adverse Events (SAE)

A serious adverse event is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death.
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the treating physician or Principal Investigator, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above should be reported as an SAE if deemed appropriate by the Principal Investigator or the Clinical Research Support Center.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas MD Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events." Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the Clinical Research Support Center, regardless of attribution (within **5 working days** of knowledge of the event).

All life-threatening or fatal events, expected or unexpected, and regardless of attribution to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the Clinical Research Support Center.

The MD Anderson "Internal SAE Report Form for Prompt Reporting" will be used for reporting to the Clinical Research Support Center.

Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory test have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse events that occur after the 30-day time period that are related to the study treatment must be reported to the Clinical Research Support Center. This may include the development of a secondary malignancy.

It is the responsibility of the Principal Investigator and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

12.0 Unblinding

In the event of an SAE (as defined above) or an emergency situation that is likely due to the symptom trial agents as determined by the treating physician or PI, a request for unblinding the symptom trial agents for the affected study subject will be sent via email to invdrugs@mdanderson.org or phoned into the Investigational Pharmacy Services at 713-792-2848. Pharmacy staff will proceed with unblinding and will contact the PI with the symptom trial agent information so that the treating clinicians can appropriately manage the SAE and confirm the specific source of the SAE. All incidents of unblinding will be documented by the study team and will also be maintained on file in the Investigational Pharmacy Services for reference. The Investigator must notify the MD Anderson IRB when unblinding occurs.

13.0 Criteria for Removal from the Study

If any of the following occur, the study medication will be stopped immediately and the patient will be removed from the study.

13.1 Development of an SAE related to the study medication

13.2 Any of these values are met or exceeded:

13.21 Alkaline phosphatase (ALP) is >2 times the upper limit of normal

13.22 Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 times the upper limit of normal

13.23 Total bilirubin > 1.5 upper limits of normal

13.24 INR > 1.5. Treating physician notified so that medical management occurs.

13.5 Signs and symptoms of severe rash (CTC version 4 > grade 3), hypersensitivity

13.6 Pregnancy during the study period.
13.7 Initiation of medication with potential interaction with minocycline, per exclusion criteria (Section 8.0).
13.8 Patient or attending physician request.

14.0 Statistical Analysis Plan

14.1 Sample Size and Randomization

The primary outcome variable is the area under the curve (AUC) using the average of the 3 most severe symptoms (pain, fatigue, and disturbed sleep) beginning at enrollment and ending 21 days postsurgery. The AUC will be calculated using trapezoidal approximation. The base of a trapezoid corresponds to the number of days between assessments while the heights correspond to 2 adjoining symptom responses. The number of trapezoids depends on the number of symptom assessments. The sum of the area for all the trapezoids represents the AUC of a particular patient.

A total of 130 patients will be randomized equally to the 2 treatment arms (minocycline or placebo).
Assuming a 7% attrition rate, we need a total of 130 patients to have 120 evaluable patients. An evaluable patient is one who provides MDASI-HN data before surgery, from at least 1 in-hospital postoperative assessment, and from at least 1 postdischarge assessment. On the basis of our longitudinal pilot data from a similar group of patients in the Head & Neck Surgery Clinic, the standard deviation of the AUC based on the average of pain, fatigue, and disturbed sleep from 2 days presurgery to 3 weeks postsurgery was 45.2. With 60 patients per treatment arm, we will be able to detect a difference of 23.5 (standardized difference of 0.52) on the symptom AUC between the 2 treatments with 81% power and a 2-sided 5% significance test.

14.2 Analysis Plan

Our emphasis is to test the efficacy of minocycline as a potential agent for reducing patient-reported symptoms in patients undergoing exploratory and/or tumor reductive surgery for head and neck cancer. Estimates of treatment effect will be obtained using standard linear regression techniques in which AUC values are regressed on indicator variables that represent treatment received. To assess the effect of patients who drop out of the study, we will use a selection model to account for informative dropouts and include the effect of age, gender, health status, Eastern Cooperative Oncology Group performance status, and disease stage as well as those baseline characteristics that are unbalanced between the dropouts and completers as covariates in the model.

We will test minocycline in its ability to reduce values of 3 symptoms (pain, fatigue, disturbed sleep). In addition to the formal evaluation of treatment effects on the primary outcome, we will also examine the prognostic effects of the type of surgery performed, histology, disease stage, performance status, age, clinical variables, strength of pain medication, and gender in predicting the outcome variable. To create the variable for strength of pain medication, we will assign a value based on the level of the most potent analgesic drug prescribed: 0, no analgesic drug; 1, a nonopioid (e.g., a nonsteroidal antiinflammatory drug or acetaminophen); 2, a weak opioid (e.g., codeine); and 3, a strong opioid (e.g., morphine). Standard exploratory data analysis techniques and descriptive statistics will be used.

Assuming that patients accrue at the rate of 5 per month, we anticipate that this study will require approximately 30 months to complete.

14.21 Primary Outcome Analysis

The primary outcome variable will be the combined AUC for selected symptoms of pain, fatigue, and disturbed sleep collected beginning at enrollment through 3 weeks postsurgery. Patients who drop out of the study after entering a week of AUC data will be included by carrying their last symptom data forward for the remaining study period under the intent-to-treat rule. The carryforward method of handling dropouts will be revisited upon completion of the study to determine if adjustments to these values can be made using longitudinal regression models estimated from patients who completed the entire study.

14.22 Secondary Outcome Analysis

We will use mixed effects model to analyze symptom burden based on the average of pain, fatigue and disturbed sleep. Other symptoms will also be analyzed individually and will be interpreted with caution due to issues associated with multiple testing and the resulting inflation of Type 1 error rates. We will explore the effect of treatment on health status. Specifically, we will use the EQ-5D dimensions as dependent variables to explore whether health status differs between patients treated with minocycline vs. placebo and to estimate these effects.

We are also interested in exploring predictors of time-to-symptom-recovery. Time-to-symptom-recovery is defined to be the time it takes for symptom severity (average of pain, fatigue and disturbed sleep) to return to preoperative levels for 2 consecutive assessments. Cox proportional hazards models will be used to explore predictors of time-to-symptom-recovery. Model building will commence by including all potential demographic and clinical variables in a a model and then using penalized likelihood method like Akaike Information Criterion (AIC) along with backward selection to remove redundant variables. Additionally, interaction between group (placebo vs. minocycline) and these predictors will be explored. Standard model fitting diagnostics will be performed. Finally, Kaplan-Meier survival curves will be plotted.

We will perform repeated measures ANOVA with group (minocycline vs. placebo), time (presurgery, postsurgery, discharge, follow up) and group-by-time interaction as factors and proinflammatory cytokine level as a dependent variable. The interaction test is of interest as we hypothesized that proinflammatory cytokine levels vary differentially over time by group. We will calculate rate of change in symptom severity for 2 weeks postsurgery and determine its relationship with proinflammatory cytokine levels and DAMPS immediately after surgery. Finally, we will use a paired t-test to determine whether there is a significant increase in DAMPS before and after surgery.

14.23 Toxicity Monitoring

All Grade 3 and 4 toxicities reported by patients in this trial will be evaluated by the treating physician and Principal Investigator, or other attending physician if Principal Investigator is not available, to determine if the toxicities were due to study medication. In the event of a Grade 3 or 4 serious adverse event that may be related to the study medication, the treating clinician will contact the Investigational Pharmacy to unblind the patient's randomization group.

To date, an active randomized placebo-controlled Phase II study of minocycline in head and neck cancer patients receiving radiation therapy (2010-0096, PI: Brandon Gunn) has reported no serious adverse events.

14.24 Interim Analysis

Three interim analyses will be performed after 25%, 50%, and 75% of the patients are evaluable. The trial will be stopped for futility if the p-value when comparing symptom AUC between the minocyline and placebo groups is greater than 0.9942 (30 patients), greater than 0.7076

(60 patients), or greater than 0.2070 (90 patients). Conversely, the trial will be stopped for superiority if the p-value when comparing the symptom AUC is less than 0.000015 (30 patients), less than 0.0031 (60 patients), or les than 0.0183 (90 patients). At the end of the trial, superiority will be claimed if the p-value is less than 0.0440. The stopping boundaries were computed using the O'Brien-Fleming approach (O'Brien & Fleming, 1979). If the numbers of patients at the interim analysis timepoints are different from above, the stopping boundaries will be adjusted using the Lan-DeMets spending function (Lan & DeMets, 1983).

14.25 Noncompliance with Study Agent

Patients who do not or cannot comply with study agent dosing requirements will remain in the study under the intent-to-treat rule.

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