Hosp Pharm 2016;51(7):535–538

www.hospital-pharmacy.com
doi: 10.1310/hpj5107–535

Off-Label Drug Uses

Minocycline: Rheumatoid Arthritis

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

Data from older controlled studies and a meta-analysis have demonstrated a beneficial effect on laboratory parameters and modest clinical effects in patients with rheumatoid arthritis (RA). Some data suggest that minocycline may be effective in patients with recent-onset disease to reduce the total steroid dose needed.[1-6]

The American College of Rheumatology (ACR) updated guideline for the treatment of RA did not include minocycline due to its infrequent use in RA and lack of new data since prior publication.[7]

RATIONALE

RA is a disease characterized by chronic inflammatory arthropathy that typically results in significant impairment in functioning and reduced quality of life. Traditionally, pharmacological management has focused on the administration of disease-modifying antirheumatic drugs (DMARDs) and, more recently, biologic agents. Early initiation of DMARDs is beneficial at minimizing long-term disability; however, their use is associated with significant adverse reactions. Tetracyclines were first used for the treatment of RA in the 1960s when the disease was thought to be caused by an infectious agent. Tetracyclines may also possess anti-inflammatory properties in addition to the antimicrobial properties that are thought to be beneficial in RA. Minocycline has demonstrated anti-inflammatory properties such as down-regulation of type 2 nitric oxide synthase (a mediator in collagen degradation), upregulation of interleukin-10 (an inhibitory cytokine in synovial tissue), and suppressive effects on B and T cell function.[1,7]

POPULATION

Adults with early and established active RA.

DOSING STUDIED

100 mg orally twice daily.[1-3,5,6]

DISCUSSION

Data from controlled studies and a meta-analysis have demonstrated a beneficial effect on laboratory parameters and modest clinical effects in patients with RA. Some data suggest that minocycline may be effective in patients with recent-onset disease to reduce the total steroid dose needed.[1-6]

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Guidelines

American College of Rheumatology

The 2015 ACR guideline for the treatment of RA is divided by duration of disease (early [RA <6 months] and established [RA ≥6 months]) and then stratified by disease activity (low and moderate or high). Recommendations are made for several DMARDs, depending on these patient factors, and include the following nonbiologic agents either alone or in combination: hydroxychloroquine, leflunomide, metho-

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trexate, and sulfasalazine. Due to infrequent use and lack of new data since the 2012 guideline, minocycline along with other nonbiologic DMARDs (azathioprine, cyclosporine, and gold) were considered but not included in the 2015 guideline. In patients with early or established RA, DMARD monotherapy is recommended as initial therapy regardless of disease severity. The guideline recommends initiating combination therapy or switching between DMARDs, biologic agents, and tofacitinib depending on duration and severity of disease and on whether deterioration, loss of benefit, or no improvement occurs. Glucocorticoids are recommended for consideration in moderate or high disease activity when initiating DMARD therapy, in DMARD or biologic failure, and for disease flares. The guideline recommends consideration of tapering but not discontinuing therapy when RA is in remission.[7]

Meta-analysis

A meta-analysis compared the effectiveness of tetracycline antibiotics versus control (placebo or conventional treatment) for reduction of disease activity in RA. Ten studies (N = 535) of patients with RA were included. Tetracyclines included oral minocycline (100 to 200 mg daily), intravenous doxycycline (200 mg daily for days 1 through 21, then 200 mg once weekly from weeks 4 through 11), oral doxycycline (200 mg daily or 50 mg twice daily), and oral tetracycline (250 mg daily). Treatment duration ranged from 11 weeks to 2 years. The majority of studies (n = 8) compared a tetracycline to placebo, and 2 studies compared to active treatment (hydroxychloroquine or methotrexate). A statistically significant benefit in favor of tetracycline treatment was observed for tender joint count (TJC) (standardized mean difference [SMD] [random-effects model] = - 0.39; 95% confidence interval [CI], -0.74 to -0.05) and swollen joint count (SMD [random-effects model] = -0.23; 95% CI, -0.41 to -0.05). Erythrocyte sedimentation rate (ESR) decreased in favor of treatment (weighted mean difference [WMD] [random-effects model] = -8.96; 95% CI, -14.51 to -3.42). A significant difference in C-reactive protein (CRP) was only observed in one study (p = .0001). No significant differences were observed with regard to patient or physician global assessment of disease severity. Only 2 studies reported on patient self-reported pain levels, and an improvement in pain score in favor of therapy was observed (SMD = -0.68; 95% CI, -1.03 to -0.33). Two studies reported on erosions and joint space narrowing, and no statistically significant differences were noted. In the studies that could be used to evaluate disability (n = 4), a small effect in favor of treatment was observed (WMD = -0.15; 95% CI, -0.28 to -0.02). No significant difference in occurrence of adverse effects was observed. The overall estimate of effect favored the treatment group (relative risk [random-effects model] = 1.78; 95% CI, 1 to 3.16). A subgroup analysis showed that minocycline alone had a greater reduction on disease activity for TJC (SMD = -0.69; 95% CI, -0.89 to -0.49) and ESR (SMD = -10.14; 95% CI, -14.72 to -5.51). The authors concluded that tetracyclines, in particular minocycline, were associated with a significant improvement in disease activity in RA with no increased risk of adverse effects.[1]

Controlled Trials

A randomized, double-blind, placebo-controlled study was conducted to determine the efficacy of minocycline in the treatment of RA. Eighty adults with active RA who were being treated or had previously been treated with at least one DMARD were administered oral minocycline (100 mg twice daily) or placebo for 26 weeks. Fifteen premature discontinuations occurred and were related to adverse effects (5 minocycline; 1 placebo), lack of efficacy (8 placebo), or concurrent illness (1 placebo). In minocycline-treated patients, changes from baseline in efficacy parameters demonstrated a significant improvement; however, when compared to placebo a significant difference was only noted for Ritchie articular index score (p = .007), number of swollen joints (p = .008), and laboratory parameters including ESR (p = .03), hemoglobin (p < .000), platelets (p < .000), CRP (p < .000), and IgM rheumatoid factor (IgM-RF) (p = .01). When all efficacy parameters were jointly analyzed, the between-group comparison was statistically significant (p < .001). Minocycline did not inhibit progression of radiologic abnormalities during the study. In the minocycline group, there were more responders to treatment (42% vs 24%; p < .05) and less treatment failures (0 vs 9 patients; p < .005). More patients experienced at least one adverse reaction in the minocycline group than in the placebo group (26 vs 11; p < .005). Adverse reactions with minocycline and placebo included nausea (20 and 5 patients, respectively), vomiting (1 patient each), increased appetite (10 and 0 patients, respectively), and dizziness (16 and 6 patients, respectively). Results of this study suggested that minocycline is beneficial and relatively safe in the treatment of RA.[2]

A larger randomized controlled trial of adults with active mild to moderate RA ($N = 219$) evaluated the safety and efficacy of minocycline (100 mg twice daily) versus placebo for 48 weeks. At study end, 79% of the minocycline group and 78% of the placebo group were receiving study medication. A significantly greater percentage of minocycline patients (compared with placebo) experienced a more than 50% improvement in joint swelling (54% vs 39%; $p = .023$) and joint tenderness (56% vs 41%; $p = .021$). No patients met American Rheumatism Association criteria for remission. Significant improvements in change from baseline were noted in the minocycline group compared to placebo for ESR (-10.8 ± 17 mm/h vs -0.7 ± 19.9 mm/h; $p < .001$), hematocrit (0.6% ± 2.6% vs -1.1% ± 4.2%; $p < .001$), platelet count (-89.6 ± 410.2 x 10^9/L vs -10.2 ± 77.7 x 10^9/L; $p < .001$), and IgM-RF (-57 ± 213 units/mL vs -17 ± 169 units/mL; $p < .001$). Nonsignificant improvements (compared with placebo) were observed in disease activity assessments by physician and patient, morning stiffness, and the Modified Health Assessment Questionnaire. Dizziness lasting longer than 1 day was reported at least once by 39% and 34% of patients in the minocycline and placebo groups, respectively. Adverse reactions lasting longer than 1 day at 48-week assessment in the minocycline and placebo groups included headache (20% and 20%, respectively), lightheadedness (11% and 10%, respectively), nausea (13% and 15%, respectively), and diarrhea (11% and 10%, respectively). Two patients in the minocycline group reported blue spots on the tongue and another reported graying teeth. Results demonstrated that minocycline was safe and effective for the treatment of mild to moderate RA. Radiographic assessments of the patients in this study were published separately and revealed that there were no significant differences in radiographic measurements, including erosion progression rate, joint space narrowing, and occurrence of newly erosive joints, between minocycline- and placebo-treated patients. The authors concluded that the short trial duration, high measurement variability, and slow rate of radiographic progression may have limited the power to detect a minocycline effect.[3,4]

In another randomized, double-blind, placebo-controlled trial, 46 adults with recent-onset (disease duration less than 12 months) RA were evaluated to determine whether minocycline (100 mg twice daily) was an effective therapy for seropositive RA. The primary endpoint was successful completion of 6 months of treatment with no toxicity and 50% improvement in composite symptoms of arthritis. One patient in the placebo group discontinued the study due to toxicity (gastrointestinal bleed) and 27 patients discontinued due to lack of efficacy. There was a significantly higher response rate in the minocycline group compared with placebo (65% vs 13%; $p < .001$). The degree of improvement from baseline for minocycline versus placebo was statistically significant for morning stiffness duration (70 ± 73 min vs 16 ± 91 min; $p = .03$), patient global status score (2 ± 2.9 vs 0.5 ± 2.7; $p = .006$), and physician global assessment score (1.6 ± 2.5 vs 0.3 ± 2.6; $p = .01$). The authors concluded that minocycline treatment was superior to placebo in patients with early seropositive RA.[5]

The efficacy of minocycline 100 mg twice daily and hydroxychloroquine 200 mg twice daily was compared in a 2-year, double-blind, randomized trial that enrolled 60 adults with recent-onset (mean disease duration less than 6 months) seropositive RA. Patients were allowed to continue their existing NSAID regimen and were started on concomitant low-dose prednisone (5 to 7.5 mg daily). The steroid dose was decreased at month 12, provided that criteria for ACR 50% improvement (ACR50) response were met. The primary endpoints were ACR50 response and steroid dose at 2 years. Significantly more patients receiving minocycline achieved ACR50 response compared with hydroxychloroquine (60% vs 33%; $p = .04$). In addition, the steroid dose was significantly lower at year 2 in those receiving minocycline (0.81 vs 3.21 mg/day; $p < .01$). Withdrawal due to toxic reactions occurred in 3 patients in the minocycline group (fingernail discoloration, dizziness, and erythematous rash) and 2 patients in the hydroxychloroquine group (gastrointestinal distress and rash). The authors concluded that minocycline was more effective than hydroxychloroquine for patients with early disease and that it most notably reduced the need for steroids.[6]

Risk/Benefit Considerations

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

Withdrawal rates in patients taking minocycline were variable. The most commonly cited reactions were nausea, diarrhea, rash, photosensitivity reactions, dizziness, headache, lightheadedness, fingernail discoloration, increased appetite, and change in taste.[2,3,5,6]

Skin discoloration has been reported with long-term use of minocycline. In a case series of 4 patients who received long-term treatment (1 to 5 years) of minocycline (100 to 200 mg daily) for the treatment of RA, blue to black discoloration occurred on the arms and legs, especially in areas where there was previous trauma.[8] In a more recent retrospective analysis of 121 patients who received at least 1 month of treatment with minocycline for RA, 36% developed documented hyperpigmentation.[9]

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