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REVIEW

Non–anti-infective Effects of Antimicrobials and Their Clinical Applications: A Review

Sapna P. Sadarangani, MBBS; Lynn L. Estes, PharmD, RPh; and James M. Steckelberg, MD

Abstract

Antimicrobial agents are undoubtedly one of the key advances in the history of modern medicine and infectious diseases, improving the clinical outcomes of infection owing to their inhibitory effects on microbial growth. However, many antimicrobial agents also have biological activities stemming from their interactions with host receptors and effects on host inflammatory responses and other human or bacterial cellular biological pathways. These result in clinical uses of antimicrobial drugs that are distinct from their direct bacteriostatic or bactericidal properties. We reviewed the published literature regarding non–anti-infective therapeutic properties and proposed clinical applications of selected antimicrobials, specifically, macrolides, tetracyclines, sulfonamides, and ketoconazole. The clinical applications reviewed were varied, and we focused on uses that were clinically relevant (in terms of importance and burden of disease) and where published evidence exists. Such uses include chronic inflammatory pulmonary and skin disorders, chronic periodontitis, gastrointestinal dysmotility, rheumatoid arthritis, and cancer. Most of these potential therapeutic uses are not Food and Drug Administration approved. Clinicians need to weigh the use of antimicrobial agents for their non–anti-infective benefits, considering potential adverse effects and long-term effect on microbial resistance.

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Antimicrobial agents are developed primarily to target pathogenic microorganisms while minimizing effects on host tissues (Ehrlich "magic bullets").[1] Mostly, unintended host effects result in adverse events; however, some non–anti-infective effects may have therapeutic benefit. We reviewed potentially beneficial non–anti-infective properties and therapeutic uses of macrolides, tetracyclines, sulfonamides, and ketoconazole. We conducted this review using a comprehensive search of PubMed between January 1, 2000, and April 25, 2014. We also reviewed selected relevant manuscripts before this timeframe identified through primary references. The following search terms were used: *anti-inflammatory effects, non–anti-infective effects, macrolides, tetracyclines, doxycycline, sulfonamides, ketoconazole, anticancer effects/properties, inflammatory pulmonary diseases, inflammatory skin disorders, prostate cancer, atherosclerosis, gastrointestinal motility, periodontitis,* and *granulomatosis with polyangiitis* (GPA, formerly known as Wegener granulomatosis). Reviews and meta-analyses, relevant clinical trials, and case series in human patients were included. Selected animal studies were included if there were key findings translatable to clinical applications. We did not include isolated case reports.

Many of these potential therapeutic uses are not Food and Drug Administration (FDA) reviewed or approved, and the quality of evidence that supports these potential uses varies widely (Table).

Many of the studies discussed focus on questions related to the efficacy of the respective non–anti-infective use. These studies have limitations regarding duration of treatment and follow-up, and, therefore, there are several unanswered questions, including long-term consequences on the microbiome, adverse effects, appropriate duration of treatment or dosing schedule, and identifying which patients would benefit most from the use of antimicrobial agents for these indications.

From the Division of Infectious Diseases (S.P.S., J.M.S.) and Hospital Pharmacy Services (L.L.E.), Mayo Clinic, Rochester, MN.

MACROLIDES

Mechanism of Action and Adverse Effects

Macrolides are part of the polyketide group of natural products. In addition to bacteriostatic effects against microbes, macrolides have

ARTICLE HIGHLIGHTS

- Antimicrobial drugs have non–anti-infective properties, including anti-inflammatory and immunomodulatory activities, which translate to numerous potential clinical applications with variable levels of evidence. The use of antimicrobials for these indications needs to be balanced with adverse effects of longer-term use and the potential for the emergence of microbial resistance. Many of these uses are not Food and Drug Administration approved. This is a novel review and summary of the use of macrolides, tetracyclines, sulfonamides, and ketoconazole for clinical uses that stem from their biological activities other than anti-infective properties.
- Macrolides have evidence for use in chronic inflammatory pulmonary disorders (eg, cystic fibrosis, non–cystic fibrosis bronchiectasis, and bronchiolitis obliterans syndrome), in inflammatory skin disorders, and in gastrointestinal dysmotility.
- Tetracyclines have evidence for use in chronic inflammatory skin disorders (eg, acne vulgaris and rosacea), periodontitis, and rheumatoid arthritis. Chemically modified tetracyclines have been studied in phase 2 trials for certain cancers.
- Sulfonamides (trimethoprim-sulfamethoxazole) have been studied for use in granulomatosis with polyangiitis (Wegener granulomatosis).
- Ketoconazole has evidence for use as an option in hormone-refractory advanced prostate cancer.

anti-inflammatory and immunomodulatory effects in humans. The immunomodulatory properties of macrolides are related to the lactone ring, which is seen with the 14-membered ring (erythromycin, clarithromycin, and roxithromycin) and the 15-membered ring (azithromycin) macrolides.[2] Macrolides inhibit the production of many proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)-α. In particular, IL-8 is a potent neutrophil activator and chemoattractant. Increased IL-8 levels in sputum and bronchoalveolar lavage fluid have been noted to correlate with severity of chronic inflammatory pulmonary disorders, specifically, cystic fibrosis (CF) and diffuse panbronchiolitis (DPB).[2] Macrolides also decrease mucus hypersecretion by inhibiting TNF-α, which stimulates mucin genes in airway goblet cells, and IL-13, which induces goblet cell hyperplasia and mucus hypersecretion.[3,4]

In addition, macrolides affect neutrophil function by decreasing oxidant production and leukotriene B formation.[3,5] They block the formation of adhesion molecules and the release of matrix metalloproteinases (MMPs) needed for neutrophil migration. Erythromycin and its derivatives also inhibit T-lymphocyte proliferation, induce T-lymphocyte apoptosis, and cause a shift from T_H1 to T_H2 response.[3,4,6]

The use of macrolides in chronic inflammatory disorders potentially requires months of therapy; therefore, the benefits of macrolides must be balanced against the potential risks of long-term administration. Adverse effects associated with long-term macrolide use include gastrointestinal adverse effects, such as nausea, vomiting, and abdominal pain due to its motilin-like activity, and hepatotoxicity. There can also be important cytochrome P (CYP) 3A4–mediated drug-drug interactions.[7,8] Macrolides are associated with QTc interval prolongation. The US FDA issued a safety announcement regarding the potential for azithromycin to cause potentially fatal arrhythmias in patients with known risk factors, such as existing QTc interval prolongation, hypokalemia, hypomagnesemia, bradycardia, or use of other anti-arrhythmic agents.[9] Ray et al[10] reported an estimated 47 additional cardiovascular deaths per 1 million courses of azithromycin compared with amoxicillin in patients with average cardiac risk, whereas those in the highest decile of cardiac risk had an estimated 245 additional cardiac deaths per 1 million courses. The use of azithromycin and death from cardiovascular causes was addressed in a large cohort study of young and middle-aged adults receiving 5 days of treatment.[11,12] Azithromycin use was not associated with increased risk of cardiovascular death compared with penicillin V use in this population (rate ratio, 0.93; 95% CI, 0.56-1.55). Although small, the potential risks of long-term macrolide use, especially in patients taking antiarrhythmic drugs or with known QTc interval prolongation, need to be balanced against possible benefit.

Data suggest that increased macrolide resistance at the population level correlates with overall macrolide use.[13] The reported rate of macrolide resistance in *Streptococcus pneumoniae* varies widely, ranging from 4% to 70%. In addition, there are reports of increases in macrolide-resistant *Mycoplasma pneumoniae*.[4] Furthermore, administering macrolides to

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TABLE. Selected Antimicrobial Drugs and Their Proposed Clinical Applications[a]

Proposed clinical application	Type of evidence	Strength of evidence[b]
Macrolides		
Chronic inflammatory pulmonary disorders		
CF	Meta-analysis and multiple RCTs with azithromycin (in patients who are colonized with *Pseudomonas aeruginosa* and those who are not) and uncontrolled studies	Accepted use • Evidence for benefit in reducing number of CF exacerbations and improvement in pulmonary infection • The durability of improved pulmonary function needs further study • CF pulmonary guidelines deem the likely benefit of macrolides in patients infected with *P aeruginosa* as moderate and in those who are uninfected as small
Non-CF bronchiectasis	Meta-analysis and multiple RCTs with erythromycin and azithromycin	Accepted use • Evidence for benefit in reducing number of exacerbations, especially in patients who have had ≥3 exacerbations in a year • Some studies have also reported improved pulmonary function
BOS	Retrospective cohort study and a meta-analysis that included 2 prospective and 8 retrospective studies	Seems promising but needs further study • Evidence for benefit in decreased risk of death if azithromycin is used in stage 1 BOS
Diffuse panbronchiolitis	Retrospective cohort studies; prospective, open-label clinical trials; and practice guidelines in Japan	Accepted use • More experience with low-dose erythromycin, with improved survival rate and pulmonary function • Beneficial effects also seen with other macrolides in smaller studies
COPD	Multiple RCTs and Cochrane review	Seems promising but needs further study • Evidence for benefit in reducing COPD exacerbations in patients with moderate COPD, and some studies have reported a modest improvement in quality of life
Asthma	RCT and Cochrane review	Insufficient evidence
Chronic inflammatory skin disorders		
Rosacea	Small clinical studies (few with a control group) and an open-label trial	Seems promising but needs further study • Suggestion of benefit; could consider as an option for treatment
Psoriasis	Small clinical studies	Insufficient evidence
Atherosclerosis	Multiple large RCTs and meta-analysis	Benefit not proven • Multiple studies have reported that macrolides do not seem to affect coronary events in patients with coronary artery disease
GI dysmotility		
GI dysmotility in the ICU setting	Small clinical studies	Needs further study; at this time, risk seems to outweigh benefit • The risk of macrolide resistance and limitation of tachyphylaxis seems to outweigh benefit of use in the ICU • ASPEN and ESPEN do not recommend routine use of macrolides for this indication
Endoscopy in upper GI bleeding	Multiple RCTs and meta-analysis	Seems promising and could be considered in certain scenarios • Erythromycin improved endoscopic visualization and reduced the need for repeated endoscopy • Further studies needed to evaluate appropriate dose and safety; could be considered in instances with severe GI bleeding, where there is likely to be blood in the stomach
Gastroparesis	Observational, open-label studies with small numbers	Insufficient evidence
Tetracyclines		
Chronic inflammatory skin disorders		
Acne vulgaris	Cochrane review and multiple small RCTs with tetracyclines (including minocycline) and SDD	Accepted use[c] • Improvement in inflammatory lesions of acne

Continued on next page

TABLE. Continued

Proposed clinical application	Type of evidence	Strength of evidence[b]
Chronic inflammatory skin disorders, continued		
Rosacea	Multiple RCTs involving tetracyclines and SDD	Possible benefit[d] • Evidence for benefit in reducing inflammatory lesions in rosacea and erythema
Ocular rosacea	Small RCTs and uncontrolled clinical trials using doxycycline or tetracycline	Possible benefit • Evidence for improvement in blepharitis • American Academy of Ophthalmology recommends use for meibomian gland dysfunction blepharitis
Periodontitis	Longitudinal double-blind studies involving SDD	Accepted use[e] • Reduced severity of periodontal disease when combined with traditional periodontal therapy
Cancer	Phase 1 and 2 clinical trials involving chemically modified tetracyclines	Insufficient evidence
RA	Meta-analysis and multiple RCTs	Needs further study • There is some evidence of benefit in reducing disease severity and joint swelling, but the role of tetracyclines in an era of newer therapeutic agents for RA is not clear
Sulfonamides		
Granulomatosis with polyangiitis	One RCT and case series	Insufficient evidence
Ketoconazole		
Advanced prostate cancer	RCT and retrospective studies	Potential benefit, further studies are needed • Ketoconazole may be one of several options for achieving stable disease or clinical response in hormone-refractory prostate cancer • American Society of Clinical Oncology and Cancer Care Ontario clinical practice guidelines deem ketoconazole a therapy that could be offered, with discussion of limited known benefit

[a]ASPEN = American Society for Parenteral and Enteral Nutrition; BOS = bronchiolitis obliterans syndrome; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; ESPEN = European Society for Clinical Nutrition and Metabolism; GI = gastrointestinal; ICU = intensive care unit; RA = rheumatoid arthritis; RCT = randomized controlled trial; SDD = subantimicrobial-dose doxycycline.

[b]Strength of evidence is based on assessment of the quality of the studies (ie, randomized clinical trials vs open-label or small observational studies), results of a meta-analysis if available, consistency of results, and, finally, the effect size and clinical significance of the findings. For example, "insufficient evidence" was used when the number of studies was small or the studies were mainly observational, with limited power. "Benefit not proven" was used if there were several large RCTs available and most of the studies did not report any beneficial effect of that antimicrobial agent for that particular clinical use. The label "accepted use" was used if there were multiple studies with consistent findings showing benefit and endorsement by clinical guidelines or approval by the Food and Drug Administration.

[c]Tetracyclines are Food and Drug Administration approved for short-term use in acne as adjunctive therapy.

[d]Subantimicrobial dosing of doxycycline (Oracea) is Food and Drug Administration approved for the treatment of inflammatory lesions of rosacea.

[e]Periostat and Alodox (SDD, 20 mg twice daily) are Food and Drug Administration approved to treat chronic periodontitis.

patients with chronic inflammatory pulmonary disorders who also have nontuberculous mycobacteria (NTM) respiratory infections selects for macrolide-resistant strains.[14] Typically, NTM infections are treated with a combination of antimicrobial drugs, and, therefore, partial treatment inadvertently may lead to resistance, thereby limiting future treatment options.[2,14]

Macrolides and Use in Chronic Inflammatory Pulmonary Disorders

Cystic Fibrosis. The CF pulmonary guidelines support the use of long-term macrolide therapy based on evidence of benefit in clinically relevant end points, such as improved lung function and decreased exacerbations, especially in patients infected with *Pseudomonas aeruginosa*.[15]

The beneficial effects of macrolides in CF are multifactorial, including their antineutrophil and anti-inflammatory activity as well as detrimental effects on the biological features of *P aeruginosa*. Many patients with CF are colonized with this organism, and *P aeruginosa* superinfection is a common complication in CF. Macrolides have poor antibacterial activity

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against *P aeruginosa* in vitro but seem to have an adjunctive role in inhibiting bacterial biofilm formation and adherence to airway mucosa, in addition to modulating host inflammatory response.[2,3,16] Macrolides inhibit the production of proinflammatory virulence factors in *P aeruginosa*. Fourteen- and 15-membered ring macrolides inhibit alginate production by mucoid *P aeruginosa* strains.[2,16] In addition, azithromycin significantly inhibited biofilm formation and alginate production by mucoid *P aeruginosa* in an in vitro study at concentrations below the minimum inhibitory concentration.[17]

Azithromycin and clarithromycin also reduce quorum sensing in *P aeruginosa* at sub—minimum inhibitory concentrations.[2,3] Quorum sensing is a mechanism of microbial intercellular communication that enables bacteria to detect and regulate population density and upregulate virulence.

A recent meta-analysis evaluated the use of azithromycin in CF. Four randomized, placebo-controlled clinical trials with a total of 368 patients were included. Forced expiratory volume in 1 second (FEV_1) and forced vital capacity were significantly increased and the number of antimicrobial courses required for acute exacerbations was significantly decreased in patients taking azithromycin. Given that macrolides as a class do not have significant antipseudomonal activity, these results cannot be attributed to a direct antibacterial effect. The risk of gastrointestinal adverse effects, however, was 72% higher with azithromycin use. There was no significant change in the microbiological profile of respiratory flora in these patients after azithromycin use.[18] Initial improvement in lung function may not be maintained in the longer-term, and this requires further study.[19]

Several clinical trials have studied the use of macrolides in patients with CF. Saiman et al[20] evaluated the use of azithromycin in a randomized, placebo-controlled trial of patients with CF who had chronic infection with *P aeruginosa*. This trial was included in the meta-analysis.[18] There were reduced numbers of infective exacerbations in the azithromycin group in this trial (hazard ratio, 0.65; 95% CI, 0.44-0.95; $P=.03$). Also, a higher rate of weight gain was noted in patients in the azithromycin arm compared with the placebo arm (mean, 0.7 kg; 95% CI, 0.1-1.4 kg; $P=.02$) at the end of the study.[20] In another randomized trial of patients with CF uninfected with *P aeruginosa*, azithromycin treatment was found to reduce pulmonary exacerbations by 50% (95% CI, 31%-79%).[21] There was also some improvement in weight gain in patients taking azithromycin but no improvement in pulmonary function.[21-23]

In summary, there is consistent evidence that macrolide therapy reduces infective exacerbations in patients with CF and may improve nutritional measures. The CF pulmonary guidelines committee deems the benefit of long-term azithromycin use in patients infected with *P aeruginosa* as moderate, and benefit is likely to be small in patients uninfected with *P aeruginosa*.[15] Therefore, a trial of macrolide therapy in such patients who may not respond to conventional therapy is recommended.[15,24] The azithromycin dose used in these clinical trials was 500 mg three times a week (or daily) in patients who weighed at least 40 kg, and 250 mg 3 times a week (or daily) for patients who weighed less than 40 kg.[18] The CF pulmonary guidelines committee recommends that patients be screened for NTM before initiation of azithromycin therapy, and screening should be repeated periodically while receiving the drug.[15]

Non-CF Bronchiectasis. Non-CF bronchiectasis is also a chronic airway inflammatory disorder, hence several trials have evaluated the use of macrolides as a potential therapeutic option.

Wong et al[25] conducted the EMBRACE trial (Effectiveness of Macrolides in Patients With Bronchiectasis Using Azithromycin to Control Exacerbations), a randomized, double-blind, placebo-controlled trial in New Zealand of patients with non-CF bronchiectasis who had at least 1 exacerbation needing antibiotic therapy in the preceding year. Patients were randomized to receive azithromycin or placebo for 6 months. The number of exacerbations requiring antibiotic therapy was reduced at 0.59 per patient in 6 months in the azithromycin group compared with 1.57 in the placebo group (rate ratio, 0.38; 95% CI, 0.26-0.54; $P<.0001$). The median time to the first exacerbation was also greater in the azithromycin group (239 days [95% CI, 190-331 days] compared with 85 days [95% CI, 52-113 days]; $P<.0001$); however, there were no significant differences in FEV_1 or quality-of-life scores. These benefits persisted for 6 months after the completion of treatment. Of note, patients were not screened for NTM

infection, and macrolide resistance testing was not routinely performed in this study.[25]

The Bronchiectasis and Long-term Azithromycin Treatment trial studied azithromycin compared with placebo for 12 months and found a reduced number of exacerbations in patients with non-CF bronchiectasis who had received azithromycin.[26] In the placebo arm, 32 of 40 patients (80%) had at least 1 exacerbation compared with 20 of 43 patients (46.5%) in the azithromycin group, yielding an absolute risk reduction of 33.5% (95% CI, 14.1%-52.96%). The number of patients needed to treat with azithromycin to maintain clinical stability was 3.0. During treatment, 88% of pathogens became macrolide resistant in the azithromycin group compared with 26% in the placebo group ($P<.001$). Azithromycin was found to be superior with respect to lung function (improved FEV_1), disease symptoms, and quality-of-life measurements. Despite the emergence of macrolide resistance, efficacy was not reduced in subsequent months.[26]

The Bronchiectasis and Low-Dose Erythromycin Study looked at twice-daily erythromycin compared with placebo for 1 year in non-CF bronchiectasis.[27] There was a modest reduction in exacerbations in the erythromycin group, with an incidence rate ratio of 0.57 (95% CI, 0.42-0.77; $P=.003$); reduced 24-hour sputum production; and an attenuated decline in lung function. However, there was an increased rate of recovery of macrolide-resistant streptococci compared with placebo (27% vs 0.04%).[27]

A recent meta-analysis[28] included the 3 aforementioned randomized clinical trials[25-27] and another smaller trial by Tsang et al.[29] The meta-analysis concluded that macrolide use was associated with significant improvement in lung function and reduced exacerbations in non-CF bronchiectasis but had no effect on quality of life. Only 3 studies had assessed the risk of macrolide resistance, and an increase in macrolide resistance was observed in 2 of them.[28]

Some authors recommend a trial of macrolide therapy for 3 to 6 months in selected patients with non-CF bronchiectasis (who have had $\geq$3 exacerbations a year) and discontinuation of macrolide therapy if there is no clear evidence of benefit in terms of reduction in exacerbation frequency.[2,3,26]

Bronchiolitis Obliterans Syndrome. Bronchiolitis obliterans syndrome (BOS) is one of the manifestations of chronic rejection after lung or bone marrow transplant and a source of morbidity and mortality in up to 25% to 50% of lung transplant recipients when it occurs.[4] The pathogenesis of BOS is unclear, but macrolides have been studied as potential therapies in prospective open-label studies and a few retrospective studies.[19]

Jain et al[30] conducted a retrospective cohort study of 178 consecutive lung transplant recipients who had developed BOS; 78 of these patients had received azithromycin. Early azithromycin use at stage 1 BOS was associated with a significantly reduced risk of death (hazard ratio, 0.29; 95% CI, 0.11-0.82; $P=.02$), which was independent of other characteristics.[30] Since then, a recent meta-analysis included 10 studies (2 prospective and 8 retrospective) of azithromycin use in BOS that had reported either percentage change in FEV_1 over time or hazard ratios for morality.[31] Most of these studies were small and lacked control groups. The study by Jain et al was included in this meta-analysis. There was a significant increase in FEV_1 with azithromycin use (mean, 8.8%; 95% CI, 5.1%-12.47%; $P<.001$). A mortality benefit was also seen with chronic azithromycin use, with a pooled hazard ratio for death of 0.25 (95% CI, 0.06-0.56; $P=.041$).[31] Some studies have found that patients who have a predominantly neutrophilic phenotype on pathologic analysis may be macrolide responsive and those with a fibroproliferative response may not.[3,4]

Diffuse Panbronchiolitis. Diffuse panbronchiolitis is a chronic airway noninfectious inflammatory disorder, most common in patients of Japanese origin. The prognosis without treatment is very poor, with 5-year mortality of 50%. Neutrophil accumulation correlates significantly with augmented neutrophil chemotactic activity in the bronchoalveolar lavage fluid of these patients.[16] Infections with *Hemophilus influenzae*, *S pneumoniae, Klebsiella pneumoniae*, and *Staphylococcus aureus* are common complications and are usually followed by colonization and infection with *P aeruginosa*.[3,16]

Kudoh et al[32] conducted a large (n=498) retrospective cohort study in Japan over 20 years comparing patients with DPB who had been taking erythromycin, 400 to 600 mg/d, with patients from earlier years who were not taking erythromycin. Erythromycin use was associated

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with a survival benefit (Cox proportional hazards regression analysis hazard ratio, 0.152; 95% CI, 0.035-0.658; P=.0118). Improved pulmonary function was also seen in a small open-label trial of 10 patients who had been taking clarithromycin, 200 mg/d, for 4 years. The mean ± SD FEV_1 increased from 1.74±0.12 L at baseline to a maximum of 2.31±0.22 L at 6 months (P<.01), and this increase was sustained over 4 years.[33]

The positive effect of macrolides in DPB seems independent of their antibacterial properties. Long-term low-dose macrolide therapy is the accepted treatment of choice for DPB, and it has had a major effect on prognosis and natural history, with improved 10-year survival from 12% to more than 90%.[3,6,16] The Diffuse Lung Disease Committee members of the Ministry of Health and Welfare of Japan endorsed the use of long-term low-dose macrolide therapy for DPB in 2000.[4,34]

Chronic Obstructive Pulmonary Disease. Macrolides have been used for antibiotic management of chronic obstructive pulmonary disease (COPD) exacerbations but have also been evaluated for their anti-inflammatory, immunomodulatory effects, as well as effects on reducing mucus secretion.

Several prospective and retrospective studies have evaluated the effect of prophylactic macrolides on the clinical course of COPD. A Cochrane review by Herath and Poole[35] in 2013 included 7 randomized controlled trials (RCTs), 5 of which used continuous antibiotics and 2 intermittent (or pulsed) courses. Participants had at least moderate COPD, and the mean age was 66 years. The primary outcomes were number of COPD exacerbations and quality of life. There was a reduction in COPD exacerbations from 69% in the placebo arm to 54% in the treatment group using continuous prophylactic antibiotics (95% CI, 46%-63%). The number needed to treat to prevent 1 exacerbation was 8 (95% CI, 5-18). There was a nonsignificant reduction in exacerbations for the pulsed treatment group (odds ratio, 0.87; 95% CI, 0.69-1.09). Both the continuous and pulsed treatment groups had a statistically significant improvement in quality of life. There was no effect on secondary outcomes of change in lung function or hospital admissions rates.[35]

Uzun et al[36] recently concluded an RCT (COLUMBUS) in the Netherlands that was ongoing at the time of the previously mentioned meta-analysis.[35] Ninety-two adults with COPD were randomly assigned to receive azithromycin (500 mg 3 times a week for 12 months) or placebo. The adjusted exacerbation rate was significantly reduced in the azithromycin group compared with the placebo group (0.58; 95% CI, 0.42-0.79; P=.001). Azithromycin was generally well tolerated; the most common adverse effect was diarrhea.[36]

These studies support the conclusion that patients with COPD who have at least moderate disease with frequent exacerbations may benefit from macrolide use as adjunctive therapy, with the goal of reducing the number of exacerbations and achieving improvement in quality of life.[3]

Asthma. Allergic and atopic responses mainly drive the chronic airway inflammation in asthma. Macrolide antibiotics, specifically, troleandomycin and erythromycin, have been studied in asthma since the 1950s and have been found to reduce corticosteroid requirements and improve sputum production and pulmonary function. Much of this effect had been attributed to troleandomycin-induced inhibition of methylprednisolone and theophylline metabolism by the hepatic CYP450 complex.[3]

However, in vitro studies have suggested that macrolides have beneficial anti-inflammatory effects that are independent of the effect on corticosteroid metabolism.[16] They are efficacious in patients without corticosteroid dependency by reducing airway hyperresponsiveness.[16] In addition, some patients with asthma have infection with *M pneumoniae* and *Chlamydophila pneumoniae* that may initiate airway inflammation, and, thus, the antibacterial activity of macrolides may be beneficial.[16,34]

The multicenter, double-blind, randomized, placebo-controlled Telithromycin in Acute Exacerbations of Asthma study evaluated the efficacy of telithromycin in acute asthma exacerbations. Short-term (10-day) treatment was used. The treatment group experienced a 40.4% reduction in asthma symptoms (evaluated using a symptom score including assessment of frequency and severity of daytime and nocturnal asthma symptoms, and their effects on daily activities) compared with 26.5% in the placebo

group (95% CI, −23.4 to −4.3, *P*=.005). There was significant improvement in FEV_1 by 0.63 L in the telithromycin group compared with 0.34 L in the placebo group (95% CI, 0.12-0.46; *P*=.001).[37]

A Cochrane review that included 7 studies concluded that there was insufficient evidence to support or refute evidence for the use of long-term macrolides in chronic asthma.[38]

Macrolides and Use in Chronic Inflammatory Skin disorders

Rosacea. The pathogenesis of rosacea is multifactorial. Clinical features include facial erythema, vasomotor instability (flushing of the face), inflammatory skin lesions, sebaceous gland overgrowth, phymatous changes, and ocular findings, including blepharitis. Conventional treatment of rosacea is based on a combination of systemic and topical antibiotic agents. Tetracyclines and erythromycin are the most commonly used oral antibiotics, mainly owing to their anti-inflammatory component.[24]

Azithromycin has been found to be of benefit in rosacea in some clinical studies, and some case reports have also shown benefit in intractable rosacea.[39-41] In some studies in which skin biopsies were performed, there was a reduction in reactive oxygen species after treatment with azithromycin.[6,42]

A randomized, open-label, clinical trial compared the efficacy of azithromycin with that of doxycycline (both given for 3 months) in 67 patients with rosacea. Clinical physician assessment was performed at baseline, monthly, and 2 months after treatment. Statistically significant clinical improvements in inflammatory lesion counts were noted with both drugs, and the study concluded that azithromycin is at least as effective as doxycycline in the treatment of rosacea.[39]

Psoriasis. In psoriasis, there is infiltration of inflammatory cells, cytokine release, and increased proliferation and turnover of keratinocytes. Streptococcal and staphylococcal antigens have been proposed as possible triggers for this disease.[43-45] The anti-inflammatory, immunomodulatory, and antibacterial properties of macrolides may, thus, theoretically be of benefit. They may also help with pruritus, although the mechanism is unknown.[6]

There have been several clinical studies regarding the efficacy of macrolides in psoriasis. Saxena and Dogra[46] conducted a blinded randomized trial of azithromycin (30 participants) over 48 weeks vs vitamin C as placebo in patients with moderate to severe chronic plaque psoriasis. There was significant improvement in skin lesions, as judged by the Psoriasis Area Severity Index score, in the azithromycin group at week 12.[46] Polat et al[47] compared the effect of erythromycin, 1000 mg/d, plus topical corticosteroids (n=36) with topical corticosteroids alone for 4 weeks in an open-label study. There was significant improvement in the mean difference in the Psoriasis Area Severity Index score at the end of the study in the group treated with erythromycin.[47]

Current psoriasis treatment guidelines focus on phototherapy, topical therapies, vitamin D analogues, and biological agents.[48] The role of traditional macrolide antibiotic agents in psoriasis needs further study.

Macrolides and Use in Atherosclerosis

It is widely accepted that atherosclerosis is an inflammatory disease that may result from an excessive immune response to various inflammatory stimuli, leading to vascular endothelial injury. Observed associations with *C pneumoniae* infection and coronary artery disease led to several studies evaluating the impact of macrolides on atherosclerosis.

In the Clarithromycin in Acute Coronary Syndrome Patients in Finland trial, 148 patients with unstable angina/non−Q-wave myocardial infarction (MI) were randomly assigned to receive clarithromycin or placebo for 3 months. There was no significant effect of clarithromycin on the primary end point, specifically, combination of death, MI, and unstable angina in the 3-month treatment period. There was an absolute risk reduction of 14.9% in the secondary end point (any cardiovascular event throughout a median of 555 days of follow-up).[49]

Similar results were seen in the Azithromycin in Acute Coronary Syndrome trial. A total of 1439 patients with unstable angina/acute MI received azithromycin (a short 5-day course) or placebo, with no difference in outcome as defined by death, recurrent MI, or recurrent ischemia necessitating revascularization at 6 months of follow-up.[50]

The WIZARD trial (Weekly Intervention With Zithromax for Atherosclerosis and Its Related Disorders) was a randomized,

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double-blind, multicenter, placebo-controlled trial with 7747 adults. Patients with previous MI and a *C pneumoniae* IgG titer greater than 1:16 received azithromycin or placebo for 12 weeks. There was no significant risk reduction in the primary event (as defined by the first occurrence of death from any cause, nonfatal reinfarction, coronary revascularization, or hospitalization for angina) in the azithromycin group compared with the placebo group after a median of 14 months of follow-up.[51]

Similarly, in the ACADEMIC (Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection With Chlamydia) study, there was no significant difference in clinical outcome (cardiovascular events) at 6 or 24 months of azithromycin therapy, but there were reductions in inflammatory markers (IL-1, IL-6, TNF, and C-reactive protein) at 6 months.[52]

The South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina was a randomized, placebo-controlled trial in patients with acute coronary syndromes with 3 arms, ie, 2 treatment groups and 1 placebo group. One treatment group consisted of amoxicillin, metronidazole, and omeprazole therapy for a week, and the other treatment group consisted of azithromycin, metronidazole, and omeprazole therapy for a week.[53] The aim of the study was to evaluate whether an amoxicillin-based regimen (targeting *Helicobacter pylori*) or an azithromycin-based regimen (targeting *H pylori* and *C pneumoniae*) would reduce markers of inflammation and affect the incidence of subsequent cardiac events in these patients. *H pylori* and *C pneumoniae* serologies were measured, as were inflammatory markers. Fifty-one percent of patients were seropositive for *H pylori,* and 41% were seropositive for *C pneumoniae*. There was a statistically significant improvement in event-free survival at 12 months for both the amoxicillin- and azithromycin-based regimens, and this effect was independent of *H pylori* or *C pneumoniae* serostatus. The reason for the reduced event rates is not clear. The authors state that there was no significant difference among the 3 treatment groups with respect to demographic variables, aspirin use, or serostatus for *H pylori* and *C pneumoniae*.[53]

The importance of non—anti-infective and immunomodulatory activities of macrolides to prevent atherosclerosis remains a matter of debate. A meta-analysis by Baker and Couch[54] in 2007 found that azithromycin does not seem to reduce recurrent cardiac events in patients with coronary artery disease.

Macrolides and Use in Gastrointestinal Motility

Gastrointestinal Dysmotility in the Intensive Care Unit Setting. Upper gastrointestinal dysmotility and ileus is a common occurrence in the intensive care unit setting from multifactorial causes, and it has a significant effect on patient recovery owing to the accompanying consequences of malnutrition, increased risk of pulmonary aspiration, and ventilator-associated pneumonia. Alterations in gut flora and changes in mucosal permeability can also lead to an increased incidence of bloodstream infections. Gastrointestinal motility is mediated by a complex interplay of endocrine and neuronal interaction, and multiple pharmacologic and nonpharmacologic approaches have been studied for the treatment of dysmotility.[55]

Erythromycin and macrolide antibiotic drugs act as motilin receptor agonists on neurons and smooth muscle cells in the enteric mucosa, especially in the gastric antrum and proximal small bowel, thus promoting motility and improving food tolerance. Erythromycin A increases the success rate of small-bowel feeding tube placement compared with placebo.[55]

When erythromycin is administered intravenously, it induces strong, high-amplitude phasic contractions that enhance gastric emptying, antral contractions, and antroduodenal coordination.[56-58] However, a study comparing metoclopramide use and erythromycin use in critically ill patients[59] found that metoclopramide was significantly better at accelerating gastric emptying in critically ill patients compared with erythromycin.[58,59]

A significant problem with macrolide treatment in gastrointestinal dysmotility is tachyphylaxis. Prolonged administration (>3-4 days) is associated with diminished efficacy, likely due to down-regulation of motilin receptors.[58] In addition, surveillance and epidemiologic studies have documented the emergence of macrolide resistance in *S pneumoniae, S pyogenes,* and viridans group streptococci, and this increase seems to correlate with macrolide use. Resistance has also been noted in Enterobacteriaciae and *H pylori*.[54]

The American Society for Parenteral and Enteral Nutrition recommends that only metoclopramide should be used for gastrointestinal dysmotility in critically ill patients because of the concern of inducing bacterial resistance with erythromycin use.[55,60,61] The European Society for Clinical Nutrition and Metabolism does not recommend routine use of erythromycin or other prokinetic agents in critically ill patients but suggests that these agents can be considered in symptomatic patients with high gastric residuals who are intolerant of enteral feeding.[55,62] Hawkyard and Koerner[55] recommend that erythromycin should be used only in situations in the intensive care unit in patients intolerant of enteral feeding who have failed other prokinetic agents.

Erythromycin Before Endoscopy in Upper Gastrointestinal Bleeding. A recent meta-analysis looked at results from 4 studies (N=269) and reported that the use of intravenous erythromycin 30 to 90 minutes before endoscopy was associated with a significant improvement in visualization of gastric mucosa (odds ratio, 4.89; 95% CI, 2.85-8.38; $P<.01$) in patients with acute upper gastrointestinal bleeding. There was a decrease in need for second endoscopy (odds ratio, 0.42; 95% CI, 0.24-0.74; $P<.01$) and a trend toward reduced units of blood transfused, which would be a surrogate marker of adequate control of bleeding during endoscopy. The dose used in these studies varied slightly from a 250-mg standard dose in 2 of 4 studies to 3 to 4 mg/kg in the other 2 studies included in the meta-analysis.[63]

In addition, a prospective, randomized, double-blind trial involving 102 patients with variceal bleeding found that endoscopic visualization was better in the erythromycin treatment group, with a completely empty stomach seen in 48.9% of the erythromycin group compared with 23.3% of the placebo group ($P<.01$). The mean endoscopic time was also shorter in the erythromycin group compared with the placebo group (19.0 vs 26.0 minutes; $P<.005$). However, the need for repeated endoscopy and the number of units of blood transfused were not statistically significantly different between the 2 groups.[64]

Gastroparesis. Gastroparesis is a chronic functional disorder of gastric motility that is often related to diabetes mellitus. It is a difficult-to-treat condition, and prokinetic agents (such as erythromycin, metoclopramide, domperidone, and serotonin agonists) are frequently used.[7] The evidence for the use of erythromycin in gastroparesis comes mainly from open-label studies with small numbers.[65] There is some evidence for improvement in symptoms.[7,65]

Potter and Snider[8] reviewed the use of azithromycin in gastroparesis. They concluded that azithromycin may prove to be an alternative prokinetic agent but that further controlled studies were needed as the current evidence is mainly from observational studies. Azithromycin has been found to have a more favorable adverse effect profile than erythromycin.[8] Neither erythromycin nor azithromycin is approved by the FDA for the treatment of gastroparesis or gastrointestinal dysmotility.

TETRACYCLINES

Mechanism of Action and Adverse Effects

Chlortetracycline, the parent compound of tetracycline, was isolated in 1947 as the natural fermentation product of the soil bacterium *Streptomyces aureofaciens,* and 6 years later it was chemically purified for the first time. Since then, semisynthetic (eg, doxycycline and minocycline) and chemically modified tetracyclines (CMTs) have been synthesized.[66,67]

Tetracyclines have additional biological activities that are independent of their antimicrobial activity, including anti-inflammatory, immunomodulatory, and antiapoptotic properties and the ability to affect cell proliferation and angiogenesis. Tetracyclines, therefore, have various potential clinical applications in diseases such as dermatitis, periodontitis, atherosclerosis, autoimmune disorders, neurodegenerative diseases, acne, cutaneous sarcoid, rheumatoid arthritis (RA), and ophthalmic disease, as well as cancer. Tetracyclines concentrate at sites of tissue injury, which is a very beneficial property clinically.[66,68]

The CMTs are tetracycline analogues that have been chemically stripped free of their antimicrobial properties but retain or even have enhanced anti-inflammatory activity. The CMT-3 (6-demethyl-6-deoxy 4 de-dimethylamino tetracycline) is the most potent inhibitor of proinflammatory mediators and of MMPs.[66]

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The exact mechanisms of action behind the non—anti-infective actions of tetracyclines are not completely known, but proposed mechanisms include (1) antioxidant properties by scavenging free radicals; (2) enhancement of BCl-2—derived effects, thereby protecting cells against apoptosis; (3) inhibition of caspase 1 and caspase 3 activation, thereby affecting the caspase-dependent apoptotic pathway; and (4) inhibition of members of the MMP family of endopeptidases, either by way of direct inhibition of MMPs from inflammatory and cancer cells or via down-regulation of expression possibly mediated via reduced inflammatory mediators.[66,68,69]

Increased MMP activity is associated with disease processes in which there is a component of inflammation and includes a few neurologic diseases, RA, tumor metastasis and invasion, and processes in heart remodeling.

Adverse effects of long-term use of oral tetracyclines include mainly gastrointestinal adverse effects (nausea, anorexia, and diarrhea), photosensitivity, and hepatic toxicity.[70,71] Tetracyclines are known to cause discoloration of teeth and enamel hypoplasia in children and so are generally contraindicated in children younger than 8 years and also in pregnant women.[72] In addition, minocycline can cause cutaneous hyperpigmentation.[70] In addition, drugs such as antacids, calcium supplements, and dairy products can impair absorption of tetracyclines by chelation if not adequately spaced.[71]

Tetracyclines and Use in Chronic Inflammatory Skin Disorders

Acne Vulgaris. The pathogenesis of acne vulgaris includes a combination of increased sebum production, altered keratinization, release of inflammatory mediators, and *Propionobacterium acnes* follicular colonization. *P acnes* seems to drive the inflammation in acne and elicits innate and acquired immune responses and production of inflammatory cytokines. It has been reported that resistance of *P acnes* to the antimicrobial effects of tetracyclines does not correlate with a negative clinical response.[73]

Skidmore et al[74] compared 26 patients receiving subantimicrobial-dose doxycycline (SDD), 20 mg twice a day, with 26 patients receiving placebo for moderate acne. The doxycycline treatment group had greater reductions in the number of inflammatory lesions, comedones, and combined inflammatory and noninflammatory lesions at 6 months. There were no statistically significant changes in microbial colony counts or antibiotic susceptibility between the 2 groups.[74] Another trial looked at 50 patients receiving doxycycline: 40 mg/d compared with 100 mg/d. Both groups demonstrated improvement; however, no comparison was performed between the groups to see whether there was any dose-response relationship, and there was no placebo group.[75]

A Cochrane review update from 2012 included 12 RCTs for the use of minocycline in acne vulgaris with a total of 39 RCTs (6013 participants).[76] Most of the trials, however, were small and deemed to be of poor quality. Minocycline was found to be an effective treatment for moderate to moderately severe acne vulgaris but no better than other commonly used acne treatments. No trials have been performed looking at the use of tetracyclines in those whose acne is refractory to other systemic therapies.[76]

All the tetracyclines seem to have similar efficacy in the treatment of acne vulgaris.[77] A systematic review evaluating data from available trials to compare the efficacy of various tetracyclines in the treatment of acne concluded there was insufficient evidence to support one tetracycline relative to another.[78] Tetracyclines are approved by the FDA for short-term treatment of acne in addition to adjunctive therapy.

Rosacea. Tetracyclines are generally used to treat the inflammatory lesions of rosacea, including erythema, papules, pustules, and blepharitis. They do not affect the sebaceous or phymatous changes that lack clinical inflammatory findings.[73]

The exact mechanisms of action of tetracyclines for rosacea are not known, but there is evidence for their benefit in this disease.[79] Although minocycline seems to be the most effective antioxidant of all the tetracyclines, current therapy favors doxycycline, which has similar efficacy for skin disorders but fewer adverse effects, such as drug hypersensitivity syndrome and hyperpigmentation.[68]

Trials using SDD, that is, less than 50 mg/d (20 mg twice daily or 40 mg controlled release), have also found benefit in the inflammatory lesions of moderate to severe rosacea. Del Rosso et al[80] conducted 2 phase 3, parallel-group, multicenter, randomized, double-blind, placebo-controlled studies comparing 40-mg

controlled-release doxycycline once a day with placebo in a group of 537 adults with moderate to severe rosacea. There was a significant decrease in inflammatory lesions in the treatment group in both studies at 3 and 16 weeks.[80] There have been 2 smaller randomized, double-blind, placebo-controlled trials conducted comparing patients receiving topical metronidazole, 0.75%, lotion combined with doxycycline, 20 mg twice a day (ie, SDD), vs topical metronidazole and placebo. Those in the doxycycline group achieved a statistically significantly greater reduction in inflammatory lesions at week 12.[81,82]

Del Rosso et al[83] conducted another study comparing doxycycline, 40 mg/d vs 100 mg/d, and there was improvement in lesions noted in both groups. There was a lower incidence of adverse events in the 40-mg group.

Subantimicrobial dosing of doxycycline is effective in treating inflammatory lesions of rosacea and has been FDA approved for this indication as Oracea (Galderma Laboratories LP). The typical duration of therapy ranges from 6 to 12 weeks.[84]

Ocular Rosacea. Ocular rosacea can appear as blepharoconjunctivitis or meibomitis, and there may also be corneal neovascularization, scarring, and keratitis.[73,85]

Bartholomew et al[86] conducted a trial in 1982 of 35 patients with ocular rosacea receiving either oxytetracycline, 250 mg twice a day, or placebo for 6 weeks. Those in the treatment arm had a statistically significantly higher chance of remission, including sustained remission at 8 months.[86]

Another prospective, randomized, double-blind, partial-crossover, placebo-controlled trial was conducted in 1995 to compare topical fusidic acid gel and oral oxytetracycline as treatment for symptomatic chronic blepharitis. Seventy-five percent of patients with blepharitis and associated rosacea were symptomatically improved by fusidic acid gel and 50% by oxytetracycline, but fewer (35%) seemed to benefit from the combination.[87]

Cumulative evidence supports tetracycline use for ocular rosacea, although more placebo-controlled prospective studies are needed using doxycycline or tetracycline.[88,89] The American Academy of Ophthalmology recommends long-term use of tetracyclines for the management of meibomian gland dysfunction blepharitis.[24,90]

Tetracyclines and Use in Periodontitis

Chronic periodontitis is among the most common chronic inflammatory diseases. Destructive periodontitis is related to infection with a complex biofilm of oral anaerobic gram-negative bacteria adherent to teeth. Persistent infection then leads to a protracted inflammatory and immune response. Patients with chronic destructive periodontitis exhibit evidence of systemic inflammation, as indicated by elevations of systemic inflammatory biomarkers.[91]

Periodontitis has been increasingly recognized as a risk factor for atherosclerotic cardiovascular disease, with the host inflammatory response being the proposed link. *Porphyromonas gingivalis*, a virulent periodontal pathogen, as part of a transient bacteremia can lead to direct invasion of blood vessels, can induce proinflammatory cytokine expression and in vitro foam cell formation, and has been seen intracellularly in blood dendritic cells in patients with acute coronary syndrome.[91]

The US National Health and Nutrition Examination Survey followed participants for 17 years and found that the presence of moderate to severe periodontitis increased the risk of coronary artery disease by 25% compared with the presence of minimal periodontal disease.[92] Theories linking chronic periodontitis and atherosclerotic cardiovascular disease (ASCVD) have included a complex series of events triggered by the immune and inflammatory responses to injury, with eventual plaque rupture and thrombosis.[91]

Owing to this increased recognition, new pharmacologic agents have been evaluated with the aim of reducing inflammation in chronic periodontitis, thereby secondarily reducing the risk of serious outcomes of ASCVD. Nonantimicrobial tetracyclines are known to have inhibitory effects on inflammatory mediators, including cytokines and MMPs, associated with both diseases.[91]

Brown et al[93] first studied the effect of SDD on inflammatory biomarkers in patients with acute coronary syndrome in the absence of dental biofilm debridement and found that a 6-month regimen of SDD significantly reduced plasma levels of high-sensitivity C-reactive protein, IL-6, and MMP-9 compared with placebo.[93]

There was no difference in the composite end point of sudden death, fatal MI, nonfatal MI, or

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troponin-positive unstable angina in SDD-treated compared with placebo-treated patients (8.4% vs 0%; *P*=.491). The periodontal status of these patients was not assessed before and after the 6-month study. Hence, it is difficult to interpret whether SDD directly reduced inflammatory mediators and MMPs in the atherosclerotic plaques in the coronary arteries or reduced the severity of inflammatory periodontal disease in these patients.[93] It is likely that SDD acts via both direct and indirect mechanisms.[91]

A nonantimicrobial low-dose doxycycline regimen combined with traditional periodontal therapy, that is, scaling and root planing, reduces the severity of periodontal disease and improves some markers of ASCVD more than scaling and root planing alone in patients with both of these local and systemic diseases.[94]

In addition, a double-blind, placebo-controlled study of patients using a 2-year regimen of SDD reported significantly increased high-density lipoprotein cholesterol levels in postmenopausal osteopenic women with periodontitis. High-density lipoprotein cholesterol particles and apolipoprotein A-I are considered cardioprotective. The mechanism by which SDD had this effect is not clear.[95]

Longitudinal double-blind studies of humans with periodontitis have reported that SDD is safe and effective.[94,96] There is some indirect evidence suggesting that treatment of chronic periodontitis may also secondarily improve ASCVD. There are FDA-approved systemically administered nonantibacterial tetracyclines, Periostat (Collagenex Pharmaceuticals) and Alodox (Lannett Company, Inc) (SDD, 20 mg twice daily), available for the treatment of chronic periodontitis. Minocycline has also been found to reduce disease progression and promote periodontal healing when given at a dose of 100 to 200 mg/d for 7 to 14 days.[68,97]

Tetracyclines and Use in Cancer

Tumorigenesis is a complex process that involves angiogenesis and tumor invasion. Recent research has found that MMPs play a central role in the initial process of invasion and in the metastatic growth of tumors such as prostate, breast, and lung cancers. These MMPs also serve as activators of growth factors and of chemoattractant proteins and, therefore, are deemed therapeutic targets in oncology. Tetracyclines affect MMPs, and, hence, there has been an interest in their use in cancer.[98]

Some of the nonantimicrobial CMT (notably CMT-3) compounds inhibited cancer cell functions in several preclinical tumor models. This has led to preliminary clinical trials in patients with advanced cancers, including breast, prostate, and lung cancers, and in patients with osteosarcomas and viral-induced sarcomas (eg, Kaposi sarcoma).[98,99]

The CMT-3 (Col-3) is a potent and specific inhibitor of cell proliferation in proliferating tumor cells and in fibroblasts and induces apoptotic cell death in tumor cells. The CMTs have antimetastatic properties, specifically to bone by inhibiting tumor cell use of MMPs to invade bone.[98,99] Also, CMT-3 has been studied in an animal model of prostate cancer reporting effectiveness in inhibiting bone metastasis.[100]

The AIDS Malignancy Consortium investigated the use of CMT-3 in treating AIDS-related Kaposi sarcoma in phase 1 and 2 studies reporting promising results in intention-to-treat analyses. The response rate in the 50-mg—dose group was 41%, which was significantly greater than the prespecified target rate of 20% (95% CI, 25%-58%; *P*=.003); the response rate in the 100-mg—dose group was 29%. The difference in response rates for these groups was not statistically significant. Further studies are needed to look at the use of tetracyclines in the treatment of Kaposi sarcoma, including an appropriate dosing strategy.[101]

The results of other phase 2 studies using CMT-3 in renal cell carcinoma and advanced soft-tissue sarcomas have been disappointing. There have been case reports of the use of SDD in lymphangioleiomyomatosis, a rare disease.[98] The application of tetracyclines in cancer is promising, but further clinical trials are needed to further define their use and role with other established treatment methods.

Tetracyclines and Use in RA

There has been interest in the use of minocycline for the treatment of RA specifically owing to its anticollagenase activity. Double-blind, placebo-controlled trials have been conducted exploring the use of minocycline in RA.[68,102,103]

Kloppenburg et al[102] found that minocycline had clinically useful anti-inflammatory properties in patients with RA and was superior to placebo in a double-blind, placebo-

controlled trial of 80 patients with active RA over 26 weeks. These patients had advanced disease and were taking a variety of disease-modifying antirheumatic drugs. The main adverse effects of minocycline use were gastrointestinal symptoms and dizziness, which led to 6 premature discontinuations.[102]

A double-blind, placebo-controlled trial conducted by Tilley et al[103] of 219 adults over 48 weeks also found minocycline treatment to be safe and effective. In patients taking minocycline vs placebo, there was improved joint swelling (54% vs 39%; $P<.023$) and improved joint tenderness (56% vs 41%).[103]

O'Dell et al[104,105] evaluated the use of minocycline in patients with RA with milder disease and shorter duration of illness in 2 separate trials. One was a placebo-controlled trial and the other used hydroxychloroquine as the comparison drug. There was a significant difference in the American College of Rheumatology 50% improvement response favoring the minocycline group in both trials.[24,104,105]

A meta-analysis in 2003 found that minocycline use had clinically significant beneficial effects in RA and in reduction of disease activity.[106] Minocycline is not FDA approved for this indication but has been used clinically as an adjunct treatment for RA in the past. The continued clinical relevance for its use in RA in an era with multiple new approaches to anti-inflammatory therapies remains to be seen.[107]

SULFONAMIDES

Mechanism of Action and Adverse Effects

Sulfonamides (trimethoprim-sulfamethoxazole) have been proposed for the treatment of GPA, but the mechanism of action that may explain their potential effects in this disease is not entirely clear. It has been postulated that trimethoprim-sulfamethoxazole has anti-inflammatory effects and can interfere with oxygen-derived free radicals. Activated, superoxide-producing neutrophils are thought to mediate the tissue destruction seen in GPA.[108,109]

Adverse effects of sulfonamides include gastrointestinal adverse effects, hepatic toxicity, and myelosuppression (either isolated neutropenia or, occasionally, pancytopenia). Renal effects include elevation in creatinine concentration (from decreased tubular secretion due to trimethoprim), hyperkalemia (due to trimethoprim blocking sodium channels in the distal tubule), and crystalluria (secondary to sulfamethoxazole in low urinary flow states). Because trimethoprim interferes with folic acid metabolism, it should not be given to patients with folic acid deficiency or to pregnant women. Trimethoprim/sulfamethoxazole is also contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency.[110,111]

Sulfonamides and Use in GPA

Granulomatosis with polyangiitis is a process with necrotizing vasculitis and granulomatous inflammation involving the upper and lower airways and can also cause necrotizing glomerulonephritis. The pathogenesis is presumed to be autoimmune, with a complex interplay of genetic, immune, hormonal, and environmental, including infectious, triggers.[112]

There have been only a few reports of using trimethoprim-sulfamethoxazole for inducing remission in GPA.[113] In addition, a few studies have suggested that trimethoprim-sulfamethoxazole therapy can prevent relapse in patients with GPA who are in remission.

The effectiveness of trimethoprim-sulfamethoxazole therapy for GPA was first suggested by DeRemee et al[114] in 1985. Stegeman et al[115] conducted a prospective, randomized, placebo-controlled study of the efficacy of trimethoprim-sulfamethoxazole given twice daily for 24 months in preventing relapses in patients with GPA in remission during or after treatment with cyclophosphamide and prednisone. Eighty-two percent of patients in the trimethoprim-sulfamethoxazole group remained in remission at 24 months compared with 60% in the placebo group (relative risk of relapse, 0.40; 95% CI, 0.17-0.98). There were fewer respiratory tract and non—respiratory tract infections in the trimethoprim-sulfamethoxazole group compared with the placebo group; these differences were statistically significant. There was no difference in the antineutrophilic cytoplasmic antibody titers throughout the study between the 2 groups.[115] In this study, 20% of patients in the trimethoprim-sulfamethoxazole group stopped treatment prematurely owing to mostly mild adverse effects.

These findings suggest that reduced relapses were perhaps due to fewer respiratory tract infections, and there is a previously reported association between nasal carriage of *S aureus*

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and an increased risk of relapse of GPA. The 7 patients who relapsed in the trimethoprim-sulfamethoxazole group relapsed in organs other than the upper respiratory tract system compared with the placebo group.[115]

It is unclear whether trimethoprim-sulfamethoxazole's possible benefit in preventing relapse in GPA might be due to its antistaphylococcal property or its anti-inflammatory effect.

KETOCONAZOLE

Mechanism of Action and Adverse Effects

Ketoconazole, an imidazole derivative, was previously used as an antifungal agent but has largely been supplanted in this role by newer triazoles. Ketoconazole's mechanism of antifungal action is inhibition of CYP450 14a-demethylase, a catalyst of conversion of lanosterol to cholesterol. Ketoconazole is a potent inhibitor of CYP450-dependent adrenal and testicular androgen. Men taking ketoconazole may get painful gynecomastia as an adverse effect due to suppression of testicular androgen production.[116]

Because of its antiandrogenic effects, there have been several trials and observational studies (summarized later herein) looking at the application of ketoconazole for androgen suppression in men with advanced and, specifically, hormone-refractory prostate cancer.[117] There is also some in vitro evidence of ketoconazole having a direct cytotoxic effect on prostate cancer cells.[118]

Notable adverse effects of ketoconazole use include nausea, vomiting, diarrhea, photophobia, thrombocytopenia, oligospermia, and impotence. The dose used in advanced prostate cancer is higher than that used for fungal infections, exacerbating the adverse effects.[116] In addition, the FDA recently issued a safety announcement alluding to risk of hepatotoxicity, adrenal insufficiency, and drug-drug interactions due to ketoconazole's potent inhibition of CYP450.[119] Other drugs can also alter ketoconazole's absorption (eg, antacids, histamine blockers, and anticholinergics) and affect its metabolism (rifampin and isoniazid).[116,120]

Ketoconazole and Use in Advanced Prostate Cancer

Androgen deprivation therapy is the standard of care for advanced prostate cancer, via either surgical or medical castration, adrenal suppression, or inhibition of androgen binding. Those who develop progressive disease after androgen deprivation therapy are considered to have androgen-independent or hormone-refractory disease. Therapeutic options for hormone-refractory prostate cancer are limited and somewhat controversial. Options include the use of adrenolytic agents, such as ketoconazole, corticosteroids, and estrogenic compounds.

As alluded to earlier, the dose of ketoconazole for the treatment of fungal infections is 200 to 400 mg/d; however, much higher doses of 1200 mg/d are used for the production of testosterone castration in advanced prostate cancer (FDA-unlabeled use).

In a phase 3 trial, patients with androgen-independent prostate cancer were randomized to receive antiandrogen withdrawal (AAWD) alone (n=132) or AAWD with ketoconazole, 400 mg 3 times a day, and hydrocortisone, 40 mg/d (n=128). Eleven percent of those with AAWD alone had a prostate-specific antigen response (decline in prostate-specific antigen level $\geq$50%) compared with 27% who were receiving AAWD with ketoconazole (P=.002). However, there was no difference in survival.[117] In another study, the overall response rate of ketoconazole as second-line therapy in 171 patients was noted to be 46%.[121]

A recent retrospective study compared matched patients with metastatic castrate—resistant prostate cancer treated with ketoconazole with those treated with abiraterone (a potent CYP17 inhibitor). Abiraterone had a statistically significantly better biochemical prostate-specific antigen response and progression-free survival. There was also better overall survival with abiraterone, although this did not reach statistical significance. The ketoconazole dose used in this study was 600 mg/d in 21 patients and 1200 mg/d in 5 patients.[122]

Ketoconazole may be one of several options to be considered in patients with hormone-refractory prostate cancer, with the goal of achieving stable disease or clinical response, and may perhaps postpone the need for more toxic chemotherapy. The American Society of Clinical Oncology and Cancer Care Ontario clinical practice guidelines deem ketoconazole to be a therapy that may be offered, accompanied by discussion of limited known benefit.[123] Further trials are needed to define comparative efficacy. In addition, owing to the inhibitory effect of

ketoconazole on adrenal corticosteroid synthesis especially with high doses, hydrocortisone replacement is needed to prevent adrenal insufficiency. The concurrent use of hydrocortisone also complicates interpretation of the therapeutic efficacy of ketoconazole in hormone-refractory prostate cancer.

CONCLUSION

A characteristic of a perfect antimicrobial agent would be that it binds specifically with receptors only on the target microorganism and has no effect on host receptors (Ehrlich "magic bullet"). However, this is rarely, if ever, achieved with currently available antimicrobial agents. Most of these agents have multiple and often clinically significant host effects as well. These host effects are generally problematic, but as noted in this review, in selected circumstances these host effects and non–anti-infective microbial effects may be used for therapeutic advantage. A few of these uses are FDA approved; many are not, and the level of evidence varies considerably among proposed therapeutic uses. There also remain numerous knowledge gaps, such as appropriate dose and duration of antimicrobials for non–anti-infective uses and effect on the emergence of microbial resistance and adverse effects. Given the potential for promoting microbial resistance and adverse events and toxicities, the clinician should carefully weigh the available evidence supporting benefit against the known risks before prescribing antimicrobial agents for these indications.

Abbreviations and Acronyms: **AAWD** = antiandrogen withdrawal; **ASPEN** = American Society for Parenteral and Enteral Nutrition; **ASCVD** = atherosclerotic cardiovascular disease; **BOS** = bronchiolitis obliterans syndrome; **CF** = cystic fibrosis; **CMT** = chemically modified tetracycline; **COPD** = chronic obstructive pulmonary disease; **CYP** = cytochrome P; **DPB** = diffuse panbronchiolitis; **ESPEN** = European Society for Clinical Nutrition and Metabolism; **FDA** = Food and Drug Administration; **FEV_1** = forced expiratory volume in 1 second; **GI** = gastrointestinal; **GPA** = granulomatosis with polyangiitis; **ICU** = intensive care unit **IL** = interleukin; **MI** = myocardial infarction; **MMP** = matrix metalloproteinase; **NTM** = nontuberculous mycobacteria; **RA** = rheumatoid arthritis; **RCT** = randomized controlled trial; **SDD** = subantimicrobial-dose doxycycline; **TNF** = tumor necrosis factor

Correspondence: Address to Sapna P. Sadarangani, MBBS, Division of Infectious Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (sapna_sad@yahoo.co.uk).

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