MAYO CLINIC

REVIEW

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

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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.

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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