CHAPTER 4

IMMUNOMODULATION WITH ANTIBIOTICS

Özgür Gündüz, MD

Introduction

"Antibiosis" defines a close relationship between two or more organisms that is hazardous at least to one of them. This kind of relationship can be observed particularly between microorganisms, forcing them to develop special traits to become more advantegous in their struggle for the vital nutrients, elimination of the competition and survival. Bacteria have shorter reproduction time than most of the organisms, giving them the advantage of rapid production to overcome the immune response of other organisms. The fungi are specialized in the synthesis of unique substances, which they can kill their rivals with. The first report of antibosis was made by Sir Alexander Fleming, in which he described the eradication of the bacteria Staphylococcus aureus by the fungi Penicillium notatum via its secretions (Penicillin) in 1926.

Antibiosis is also one of the prominent factors underlying the bacterial mutations. Bacteria mutate to become more resistant to the detrimental effects of the substances secreted by fungi, the so-called "antibiotics". A more precise definition of "antibiotics" is that they are substances produced by one microorganism that selectively inhibits the growth of another. In the course of time, this definition has been changed to cover semi-synthetically produced antibacterial drugs. Microorganisms can also become resistant to these semi-synthetic molecules and render their antimicrobial effects useless, causing huge amounts of money and efforts to be invested in development of new antimicrobial agents. But, that does not mean the "old" antibiotics are no longer useless. Far from it, with the discovery of the new modes of action of the antibiotics, particularly anti-inflammatory effects, it seems these drugs will be in use for a long time. This text summarizes notable antibiotic groups and their immunomodulatory effects.

Macrolides

This class of antibiotics consists of erythromycin, roxythromycin, clarithromycin, azithromycin, and spiramycin. They possesss a macrocyclic lactone ring, which consists of 14 to 16 atomic members. Their main mechanism of antimicrobial action is inhibition of bacterial protein synthesis. Macrolides bind to 50S subunit of the ribosomes and interfere the translocation of the growing polypeptide chain from the acceptor site (A-site) to the peptidylsite (P-site or donor site). They have a wide spectrum, which covers gram-positive cocci (except methicillin resistant *Staphylococcus aureus* – MRSA), Legionella pneumophila, Campylobacter jejuni, Mycobacterium avium-intracellulare, Helicobacter pylori and also the bacteria without cell walls, *Chlamidia*, *Mycoplasma* and *Ureaplasma species*. Since *C.pneumonia*, *M.pneumonia* are among the most common bacterial pathogens associated with community-acquired pneumonia, macrolides have become one of the most prescribed antibiotics in clinical practice. Particularly, azithromycin has been found to be very effective[1]. They are also frequently used to treat infections of upper respiratory tract and skin.

First observation of immunomodulatory effects of the macrolides was reported in 1987.[1] Kudoh et al reported a marked improvement in clinical symptoms and increased life expectancy in patients with diffuse panbronchiolitis (DPB), an inflammatory airway disorder with a rapid progression and poor prognosis, treated with eryhtromycin. Serum erythromycin level measurements were below the minimal inhibitory concentrations, which led the researchers to associate these clinical improvements with possible anti-inflammatory properties of erythromycin rather than its antibacterial effects. Since then, numerous studies also confirmed the observations of Kudoh et al. As of today, not only macrolides, but several other antibiotics have been shown to possess anti-inflammatory and/or immunomodulatory properties.

Macrolides are known to exert their effects on the immune system on various levels. They have been shown to modulate the production of proinflammatory cytokines (interleukin (IL)-1, IL-2, (interferon) IFN-γ, (tumor necrosis factor) TNF-α, etc) and anti-inflammatory cytokines, (IL-10, transforming growth factor (TGF)-β,etc).[3] In vivo studies indicate that inhibitory effects of macrolide antibiotics on proinflammatory cytokines are particularly evident in patients with cystic fibrosis (CF) and asthma.[4,5]

Macrolides also stimulate the phagocytotic abilities

In 2011, Dhand and et al. reported rapid clearanceof persistant bacteriemia due to methicillin-resistant Staphylococcus aureus (MRSA) via combined use of anti-staphylococcal β-lactams and daptomycin.[39] A subsequent study by Sakoulas and et al. revealed similar results. Sakoulas et al. proposed that nafcillin facilitates the killing of MRSA by innate immune system by sensitizingthe bacteria) to host defense proteins (HDPs), particularly to cathelicidin LL-37.[40]

Fluoroquinolones

This class of antibiotics inhibit several enzymes involved in the biosynthesis of bacterial deoxy-ribonucleic acid (DNA). Primary targets of fluoroquinolones are DNA gyrase, also known as topoisomerase II, and topoisomerse IV. DNA gyrase relaxes the supercoiled DNA, which occurs during the unwinding of DNA by the enzyme helicase. Topoisomerase IV unlinks the bacterial DNA after its replication. (Gemifloxacin targets both of these enzymes). Besifloxacin, ciprofloxacin, gatifloxacin, norfloxacin, levofloxacin, moxifloxacin, and ofloxacin are the other members of fluoroquinolone antibiotics. The spectrum of early quinolones, cipprofloxacine, covers gram-negative bactreria, i.e. Pseudomonas aeruginosa, Haemophilus influenza, Moraxella catarrhalis. They are predominantly used to treat urinary tract infections. The newer ones (group IV – I.E., moxifloxacin, gemifloxacin) have a wider coverage and are effective against gram-positive bacteria, atypical bacteria, such as *Streptococcus, Chlamidya pneumoniae, Mycoplasma pneumonia* and also some anaerobs. Except central nervous system, fluoroquinolones can penetrate into all other tissues and body compartments and therefore, they are frequently used to treat to infections of skin, bone, intra-abdominal cavity and also pneumonia. Their prominent side-effects are cartilage toxicity, increase risk of Steven-Johnson syndrome, prolonged QT syndrome and tendinitis.

Most reports regarding the immunomodulatory properties of quinolones come from in vitro studies with lipopolysaccharide-stimulated human monocytes. Inhibitory effects of many fluoroquinolones (i.e., ciprofloxacin, trovafloxacin, moxifloxacin, grepafloxacin, and levofloxacin) on proinflammatory cytokines (IL-1α, IL-1β, TNF-α, IL-6, and IL-8) have been reported.[41 – 47] In a similar study, Weiss et al. have also reported inhibition of IL-8, TNF-α, and IL-1β in LPS-stimulated human peripheral blood monocytes and in the THP-1 monocytic cell line with moxifloxacin and proposed inhibition of major inflammatory signal transduction pathways (NF-κB and mitogen-activated protein kinase activation) as a possible underlying mechanim.[48] Similar outcomes were also reported by Shalit et al in when they treated immunocompromised rats with moxifloxacin after intratracheal Candida albicans injection.[49] They found significantly decreased levels of IL-8, TNFα and IFNγ in lung tissue.

Conclusion

Over the last 20 years, clinical and experimental evidence regarding immunomodulatory properties of antibiotics is steadily increasing. Relevant reports are coming from a wide spectrum of studies. Although most of them have been observed in vitro settings, there are also very promising clinical observations – i.e., doxycyclin in stroke patients- , which be the first stepstones to form immunomodulatory treatment regimens with classical antibiotics.

REFERENCES

1. Noguchi S, Yatera K, Kawanami T, Yamasaki K, Uchimura K, Hata R, Tachiwada T, Oda K, Hara K, Suzuki Y, Akata K, Ogoshi T, Tokuyama S, Inoue N, Nishida C, Orihashi T, Yoshida Y, Kawanami Y, Taura Y, Ishimoto H, Obata H, Tsuda T, Yoshii C, Mukae H. Efficacy and safety of azithromycin infusion in patients with mild or moderate community-acquired pneumonia. .Jpn J Antibiot. 2014; 67(3):193-203.
2. Kudoh S, Uetake T, Hagiwara K. Clinical effects of low-dose long-term erythromycin chemotherapy on diffuse panbrochiolitis. Nihon Kyobu Shikkan Gakkai Zasshi 1987;25: 632-642.
3. Culic O, Erakovic V, Parnham MJ. Anti-inflammatory effects of macrolide antibiotics. Eur J Pharmacol 2001;429:209-229.
4. Equi A, Balfour-Lynn IM, Bush A. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial. Lancet 2002; 360: 978–984.
5. Kraft M, Cassell GH, Pak J.Mycoplasma pneumoniae and Chlamydia pneumoniae in asthma: effect of clarithromycin. Chest 2002; 121: 1782–1788.
6. Yamaryo T, Oishi K, Yoshimine H. Fourteen-member macrolides promote the phosphatidylserine receptor-dependent phagocytosis of apoptotic neutrophils by alveolar macrophages. Antimicrob Agents Chemother 2003; 47: 48–53.
7. Hodge S, Hodge G, Jersmann H. Azithromycin improves macrophage phagocytic function and expression of mannose receptor in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2008; 178: 139–148.
8. Tamaoki J, Nakata J, Tagaya E. Effects of roxithromycin and erythromycin on interleukin 8-induced neutrophil recruitment and goblet cell secretion in guinea pig tracheas. Antimicrob Agents Chemother 1996; 40: 1726–1728.
9. Tsai WC, Rodriguez ML, Young KS. Azithromycin blocks neutrophil recruitment in Pseudomonas endobronchial infection. Am J Respir Crit Care Med 2004; 170: 1331–1339.
10. Piacentini GL, Peroni DG, Bodini A. Azithromycin reduces bronchial hyperresponsiveness and neutro-philic airway inflammation in asthmatic children: a preliminary report. Allergy Asthma Proc 2007; 28: 194–198.
11. Sakito O, Kadota J, Kohno S. Interleukin 1 beta, tumor necrosis factor alpha, and interleukin 8 in bronchoalveolar lavage fluid of patients with diffuse panbronchiolitis: a potential mechanism of macrolide therapy. Respiration 1996; 63: 42–48.
12. Suzuki H, Shimomura A, Ikeda K. Effects of long-term low-dose macrolide administration on neutrophil recruitment and IL-8 in the nasal discharge of chronic sinusitis patients. Tohoku J Exp Med 1997; 182: 115–124.
13. Verleden GM, Vanaudenaerde BM, Dupont LJ. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with

bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2006; 174: 566–570.

14. Khair OA, Devalia JL, Abdelaziz MM. Effect of erythromycin on Haemophilus influenzae endotoxin-induced release of IL-6, IL-8 and sICAM-1 by cultured human bronchial epithelial cells. Eur Respir J 1995; 8: 1451–1457.
15. Sanz MJ, Nabah YN, Cerdá-Nicolás M, O'Connor JE, Issekutz AC, Cortijo J, Morcillo EJ. Erythromycin exerts in vivo anti-inflammatory activity downregulating cell adhesion molecule expression. Br J Pharmacol. 2005; 144(2):190-201.
16. Mitsuyama T, Tanaka T, Hidaka K, Abe M, Hara, N. Inhibition by erythromycin of superoxide anion production by human polymorphonuclear leukocytes through the action of cyclic AMP dependent protein kinase. Respiration 1995, 62, 269-273.
17. Abdelghaffar H, Vazifeh D, Labro MT. Comparison of various macrolides on stimulation of human neutrophil degranulation in vitro. J Antimicrob Chemother 1996; 38: 81–93.
18. Culic O, Erakovic V, Cepelak I. Azithromycin modulates neutrophil function and circulating inflam-matory mediators in healthyhuman subjects. Eur J Pharmacol 2002; 450:277–289.
19. Labro MT, el Benna J, Babin-Chevaye C. Comparison of the in-vitro effect of severalmacrolides on the oxidative burst of humanneutrophils. J Antimicrob Chemother 1989;24: 561–572.
20. Abdelghaffar H, Vazifeh D, Labro MT. Erythromycin Aderivedmacrolides modify the functional activities of human neutrophilsby altering the phospholipase D-phosphatidate phosphohydrolase-transduction pathway: L-cladinose is involved both in alterationsof neutrophil functions and modulation of this transductionalpathway. J. Immunol. 1997, 159, 3995-4005.
21. Aoshiba K, Nagai A, Konno K. Erythromycin shortens neutrophil survival by accelerating apoptosis. Antimicrob Agents Chemother 1995; 39: 872–877.
22. Inamura K, Ohta N, Fukase S: The effects of erythromycin on human peripheral neutrophil apoptosis. Rhinology 2000; 38: 124–129.
23. Kawakami K, Kadota J, Iida K. Phenotypiccharacterization of T cells in bronchoalveolarlavage fluid (BALF) and peripheral bloodof patients with diffuse panbronchiolitis: theimportance of cytotoxic T cells. Clin ExpImmunol 1997; 107: 410–416.
24. Brambrink AM, Koerner IP, Diehl K, Strobel G, Noppens R, Kempski O. The antibiotic erythromycin induces tolerance against transient global cerebral ischemia in rats (pharmacologic preconditioning). Anesthesiology 2006;104: 1208-1215.
25. Koerner IP, Gatting M, Noppens R, Kempski O, Brambrink AM. Induction of cerebral ischemic tolerance by erythromycin preconditioning reprograms the transcriptional response to ischemia and suppresses inflammation. Anesthesiology 2007, 106: 538- 547.
26. Suomalainen K, Sorsa T, Golub LM, Ramamurthy N, Lee HM, Uitto VJ, Saari H, Konttinen YT. Specificity of the anticollagenase action of tetracyclines: relevance to their antiinflammatory potential. Antimicrob Agents Chemother 1992, 36: 227-229.
27. Gabler WL, Smith J, Tsukuda N.Comparison of doxycycline and a chemically modified tetracycline inhibition of leukocyte functions. Res Commun Chem Pathol Pharmacol 1992;78(2):151-60.
28. Van Lint P, Libert C. Chemokine and cytokine processing by matrix metalloproteinases and its effect on leukocyte migration and inflammation. J Leukoc Biol 2007; 82 (6): 1375–81.
29. McCarty M, Fivenson D. Two decades of using the combination of tetracycline derivatives and niacinamide as steroid-sparing agents in the management of pemphigus: defining a niche for these low toxicity agents. J Am Acad Dermatol. 2014;71(3):475-9.
30. Jiang Y, Zhu J, Wu L, Xu G, Dai J, Liu X.Tetracycline inhibits local inflammation induced by cerebral ischemia via modulating autophagy. PLoS One. 2012;7(11):e48672
31. Edan RA, Luqmani YA, Masocha W. COL-3, a chemically modified tetracycline, inhibits lipopoly-saccharide-induced microglia activation and cytokine expression in the brain. PLoS One 2013; 8(2):e57827
32. Lai AY, Todd KG. Hypoxia-activated microglial mediators of neuronal survival are differentially regulated by tetracyclines. Glia 2006; 53(8):809-16.
33. Lampl Y, Boaz M, Gilad R, Lorberboym M, Dabby R, Rapoport A, Anca-Hershkowitz M, Sadeh M. Minocycline treatment in acute stroke: an open-label, evaluator-blinded study. Neurology 2007; 69(14):1404-10.
34. Tilakaratne A, Soory M. Anti-inflammatory Actions of Adjunctive Tetracyclines and Other Agents in Periodontitis and Associated Comorbidities. Open Dent J 2014; 8: 109-24.
35. Tauber SC, Nau R. Immunomodulatory Properties of Antibiotics. Curr Mol Pharmacol 2008; 1:68-79.
36. Periti, P. Immunopharmacology of oral betalactams. J Chemother 1998, 10, 91-96.
37. Scheffer J, Konig W. Cephalosporins and inflammatory host reactions. Respiration 1993;60(Suppl. 1): 25-31.
38. Mangano K, Quattrocchi C, Aiello C, Scalia, G, Speciale A, Nicoletti G, Di Marco R. Immunomodulatory properties of cefaclor: in vivo effect on cytokine release and lymphoproliferative response in rats. J Chemother 2006;18, 641-647.
39. Dhand A, Bayer AS, Pogliano J, Yang SJ, Bolaris M, Nizet V, Wang G, Sakoulas G. Use ofantistaphylococcal beta-lactams to increase daptomycin activity in eradicating persistentbacteremia due to methicillin-resistant Staphylococcus aureus: role of enhanced daptomycinbinding. Clin Infect Dis. 2011; 53: 158–163.
40. Sakoulas G, Okumura CY, Thienphrapa W, Olson J, Nonejuie P, Dam Q, Dhand A, Pogliano J, Yeaman MR, Hensler ME, Bayer AS, Nizet V.Nafcillin Enhances Innate Immune-Mediated Killing ofMethicillin-Resistant Staphylococcus aureus. J Mol Med (Berl) 2014; 92(2): 139–149.
41. Araujo, FG, Slifer TL, Remington JL Effect of moxifloxacin on secretion of cytokines by human monocytes stimulated with lipopolysaccharide. Clin. Microbiol. Infect.2002; 8: 26–30.
42. Bailly S, Mahe Y, Ferrua B, Fay M, Tursz T, Wakasugi H, Gougerot-Pocidalo MA. Quinolone-induced differential modification of IL-1 alpha and IL-1 beta production by LPS-stimulated human monocytes. Cell Immunol 1990; 128(1):277-88.
43. Choi JH, Song MJ, Kim SH, Choi SM, Lee DG, Yoo JH, Shin WS. Effect of moxifloxacin on production of proinflammatory cytokines from human peripheral blood mononuclear cells http://www.ncbi.nlm.nih.gov/pubmed/146384692003; 47(12):3704-7.
44. Khan AA, Slifer TR, Remington JS. Effect of trovafloxacin on production of cytokines by human monocytes. Antimicrob Agents Chemother 1998; 42(7):1713-7.
45. Ono Y, Ohmoto Y, Ono K, Sakata Y, Murata K. Effect of grepafloxacin on cytokine production in vitro. J Antimicrob Chemother 2000; 46(1):91-4.
46. Williams AC, Galley HF, Webster NR. The effect of moxifloxacin on release of interleukin-8 from human neutrophils. Br J Anaesthesiol 2001; 87: 671–672.
47. Zhao D, Keates AC, Kuhnt-Moore S, Moyer MP, Kelly CP, Pot-

houlakis C. Signal transduction pathways mediating neurotensin-stimulated interleukin-8 expression in human colonocytes. J Biol Chem 2001; 276(48):44464-71.

48. Weiss T, Shalit I, Blau H, Werber S, Halperin D, Levitov A, Fabian I. Anti-inflammatory effects of moxifloxacin on activated human monocytic cells: inhibition of NF-kappa B and mitogen-activated protein kinase activation and of synthesis of proinflammatory cytokines. Antimicrob Agents Chemother 2004; 48:1974-1982.

49. Shalit I, Horev-Azaria L, Fabian I, Blau H, Kariv N, Shechtman I, Alteraz H, Kletter Y. Immunomodulatory and protective effects of moxifloxacin against Candida albicans-induced bronchopneumonia in mice injected with cyclophosphamide. Antimicrob Agents Chemother 2002; 46:2442-2449.