



MINIREVIEW: PROSPECT OF DOXYCYCLINE IN SYSTEMIC LUPUS ERYTHEMATOSUS TREATMENT

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ABSTRACT

Doxycycline has non-antibiotic effects which are necessary for lupus treatment, such as immunosuppressive, anti-inflammatory, and anti-depressive effects. This widely used drug is a promising one to be developed as lupus drug since doxycycline has no data of its microbial resistance and it is safe for maternity. The other benefit is that doxycycline has lower side effects than the current drugs for lupus treatment. It gives excellent chances for women with lupus to be pregnant and have healthy babies. This article contains the compilation data of doxycycline target sites beyond its beneficial activities for lupus and also its limitations. Finally, this data will be a background for doxycycline in lupus drug development.

Keywords: doxycycline, non-antibiotic effects, lupus, drug development, maternity

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INTRODUCTION

Systemic lupus erythematosus or lupus is an autoimmune disease that has many therapy problems. The drug choices in the guidelines for daily lupus treatments are limited to the unsafe off-labeled drugs such as cytotoxic, antimalaria, and corticosteroid drugs [1,2]. The side effects might be severe and harmful because the drugs are routinely used in long-term treatment. The cytotoxic drugs have a lot of side effects, such as in blood, nerves,

gastro-intestine, and fertility. The side effect of anti-malarial drugs is toxic to eye nerves. Meanwhile, the corticosteroids promote so many metabolic disorders [3]. These data reveal the need for the safe drugs for lupus.

The potential old and widely used drug which has beneficial effects on lupus is doxycycline. It has non-antibiotic effects which support the stability of lupus-patient condition. The immunosuppressive and anti-inflammatory [4,5] occur since it can

inhibit the matrix-metalloproteinase-9 as its target site [6–8]. This MMP-9 is crucial in the development of lupus severity, so it must be inhibited [9]. Additionally, the data of antidepressant effect of doxycycline [10,11] supports the efficacy to be applied in lupus treatment, because stresses are leading factors which make the lupus manifestations appear more often. Doxycycline does not affect the patients' fertility, blood, nerves, and others [12], but it has some side effects in gastrointestinal tract [13] like others antibiotics. However, the side effect is mild and can be handled well.

Thus, this article will briefly review the benefits and harms of doxycycline, based on its target site, if doxycycline applied in lupus patients. The evident-based data of antibiotics, especially tetracycline derivatives, in osteoarthritis and rheumatoid arthritis is huge support for developing doxycycline to be a new choice for lupus drug treatment.

THE HISTORY OF DOXYCYCLINE NON-ANTIBIOTIC ACTIVITIES

Doxycycline is a derivate of tetracycline, a wide spectrum antibiotic. Tetracycline was obtained in the 1950s with a single indication as antibiotic for acne. Then, in the next research, the tetracycline derivatives with longer half-life were found in 1961 (minocycline) and 1976 (doxycycline) [14]. Moreover, the other effects of this tetracycline derivatives were obtained by time. Now, it is widely used for many indications, such as to treat rosacea, bullous dermatoses, neutrophilic diseases, pyoderma gangrenosum, sarcoidosis, aortic aneurisms, cancer metastasis, periodontitis, and autoimmune disorders rheumatoid arthritis, and scleroderma [15].

The use of antibiotics in autoimmune disorders is based on the premise that infection plays a role in triggering autoimmune reaction called

“molecular mimicry,” “epitope spreading,” or “bystander activation.” This link could occur directly and indirectly [15]. Based on it, tetracyclines is suggested as a drug candidate for rheumatoid arthritis by scientists which expect that mycoplasma infection lead to rheumatoid arthritis [16]. The use of tetracycline, minocycline, and doxycycline was continued until the clinical study punished in the 1990s. Then, it was found that preliminary evidence indicate that doxycycline may also exert anti-inflammatory [17] and antioxidant activities. Doxycycline is more acceptable for therapies since minocycline indicates a cytotoxic side effect.

DOXYCYCLINE MAIN TARGET SITES

Doxycycline Effects on Anti-nociceptive and Inflammatory Cytokines

Lupus is a systemic inflammation disorder with the increase of inflammation mediators [8,18,19]. Some experiments result in anti-inflammatory data of doxycycline. The inflammatory biomarkers used are IL-1 β , IL-6, IL-8, and TNF- α . Doxycycline in the concentration of 2 μ M significantly reduces IL-1 β , IL-8, and TNF- α ($p < 0.05$) expression. Moreover, the IL-6 can be reduced in the concentration of 10 μ M. The results show the doxycycline ability to regulate the release of inflammation mediators by host cells. The subantimicrobial doses of doxycycline also reduce PAR₂, IL-17, TNF- α , and mRNA expression of IL-1 β ($p < 0.05$) due to its MMP inhibition [5,20,21]. It shows that the low doses of doxycycline correlated to the modulation of pro-inflammatory genes. Doxycycline reveals independent effects, such as the inhibitions of MMPs [7,22], nitric oxide synthase (NOS) [4], tumor progression and bone resorption, angiogenesis, and inflammation [21].

The anti-inflammation effect is briefly explained by Leite [4] based on the experiments that show that doxycycline can reduce the release of prostaglandins, proteases, lysosomes, histamine, and serotonin. It is also effective to reduce the neutrophil migration in the peritoneal cavity like non-steroid anti-inflammatory drugs. This data is supported data [19,23] that states doxycycline reduce the myeloperoxidase in human neutrophil significantly. The antinociceptive effect also present in the dose of 50 and 100 mg/kg BW [18].

Impacts on MMP-9

Matrix metalloproteinase-9 (MMP-9) plays an essential role in lupus and the level increase significantly in lupus patients (9,24–26), so it can be a targeted therapy for lupus. In this case, doxycycline can inhibit the MMP-9. MMPs are zinc-dependent proteases which can degrade or modify the extracellular matrix components, including angiogenesis, neurogenesis, remodeling regeneration and synaptic plasticity, inflammatory and epilepsy [7]. Doxycycline affects specifically on MMP-9 in therapeutic doses [27].

One of the lupus manifestations is arthritis, which known as lupus arthritis. In this case, it has been found that doxycycline inhibits osteoclastogenesis along with the suppression of MMP-9 activity without affecting the expression of the MMP-9 protein [28]. Additionally, close to MMP-9, Hanemaaijer [27] also states based on his in vivo study that doxycycline down-regulates MMP-8 (neutrophil collagenase) at both the mRNA and protein levels. It causes the inhibition of cartilage degradation at the target joints.

In the other manifestations, such as lupus neural disorder, doxycycline also shows its benefit. It has been found that doxycycline could aggravate the absence-like epileptic seizures in vivo, via MMPS

inhibition [7]. Also, doxycycline can reduce a depressive-like behavior in an in vivo study performed by Mello [11]. The results show that doxycycline is comparable to imipramine to ameliorate the depressive-like behavior, reveal its anti-depressive activity in human.

THE USE OF DOXYCYCLINE IN OTHER INFLAMMATORY DISEASES

Osteoarthritis (OA)

Brandt [28] reports the results of his double-blind trial of doxycycline at the dose of 100 mg twice a day in osteoarthritis patients. The joint space narrowing (JSN) in this experimental subjects were measured after 30 months treatment. Meanwhile, the severity joint pain was measured every 6 months. After 16 months treatment, the mean of JSN and joint index of the doxycycline group is 40% lower than the placebo. After 30 months treatment, it is only 33% lower than the placebo effect which is suggested as a floor effect. In addition, based on the follow-up, the progress of index knee can be inhibited by the use of doxycycline. This case can be a consideration of the use of doxycycline in lupus arthritis.

Rheumatoid Arthritis (RA)

Shehwaro [29] compared the efficacy of doxycycline in combination with methotrexate in early seropositive rheumatoid arthritis subjects. The results show that the combination increases the treatment outcome. Based on the parameter of American College Rheumatology 50% (ACR50), the low dose of doxycycline can increase the ACR 50 response of methotrexate three times higher than the single use of methotrexate. Moreover, the high dose of doxycycline can only add three percent higher than the low dose. However, the mechanism of this effect is not understood. It might be correlated to

MMPs inhibition and immunomodulatory activity of doxycycline. This data is supported by Grimsen's data [30], which states that the combination of doxycycline and alpha-1 antitrypsin can reduce the arthritis development significantly due its expression of IL-6, macroscopic appearance, and its tissue structure.

Nasal polyps

The other use of doxycycline is in the treatment of chronic rhinosinusitis and nasal polyps. Doxycycline reveals its moderate effect which lasted for 12 weeks. The duration is longer than the effect of methylprednisolone. Doxycycline significantly reduces the levels of myeloperoxidase and matrix metalloproteinase-9 in nasal secretions [31].

CONSIDERED PROBABLE SIDE EFFECTS

Extracellular signal-Regulated Kinases (ERK) defect

Doxycycline induces ERK defect which results in demethylation and overexpression of methylation-sensitive genes, and then it induces lupus-like autoimmunity in mice [32]. This result is in line with the other research [33] about the effect of diet on the lupus manifestations induced by doxycycline. The use of doxycycline results in the presence of anti-dsDNA, but it cannot result in lupus-like organ damage and disease. Obradovi [6] explains that doxycycline inhibits the capacity of IL-17 to induce MMP-9 expression in myoblast cells by regulating the activation of ERK 1/2. It also protects C2C12 myoblast cells so that it may be useful for inflammatory diseases. However, this ambiguous data need other research to confirm the real fact.

Acute Pancreatitis

Doxycycline could be one leading factor of acute pancreatitis. It is based on a case study which [34] states that doxycycline might be a cause of acute pancreatitis, but the data cannot be generalized since it is only a case and the patient also use other drugs which had side effects in pancreas too.

Gastrointestinal Injury

The gastrointestinal disorder is a common side effect of antibiotics. Doxycycline leads to small vessel injury with fibrinoid material around the vessel in most patients, and a few patients had similar changes in the duodenum [13]. The information will improve patient awareness if they use doxycycline in long-term treatment.

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