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Research Article

The Fibrotic Process and the Reverse in Deposition of Connective Tissue and the Fibrotic Tissue What is the Role Played by Ciprofloxacin and Derivates? it is a Class Effect: Related the Antimicrobial Properties or Additional Separate Effect?

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Abstract:

Aim of this research is to verify the properties of ciprofloxacin and other fluorochinolon in reverse the connective tissue deposition and the fibrotic process starting from the experice of Wong et al. After a review of the scientific literature the focus is to verify if this effect is due to the antimicrobial effect of this molecule or there are other mechanims of action involved. The same the role played by the time in this process. Even if the fibrotic process was hystorically considered irreversible new evidence show other. A global conclusion is then submitter to the researcher for future investigation.

Keywords: fluorochinolon; reverse of the fibrotic process; connective tissue deposition; mechanism of action; side effetcs; adverse event; structure activity relationship; physiology; pathology; oncology

Introduction

According to molecular biology and clinical research on the reversibility of scarringit is possible to verify that: Early/Dynamic Stage: In conditions like early-stage hepatic or pulmonary fibrosis, stopping the initial injury (removing toxins in the liver or exposure in the lungs) allows the body to break down excess scar tissue. Advanced/Terminal Stage: In advanced diseases like Idiopathic Pulmonary Fibrosis (IPF) or liver cirrhosis, scars mature into paucicellular lesions with highly cross-linked collagen and elastin, making them functionally irreversible.

According Neil C Henderson et al 2020

"Fibrosis can affect any organ and is responsible for up to 45% of all deaths. It has long been thought to be relentlessly progressive and irreversible, but both preclinical models and clinical trials in various organ systems have shown that fibrosis is a highly dynamic process. This has implications for therapeutic interventions that are designed to capitalize on this inherent plasticity. But despite substantial progress in our understanding of the pathobiology of fibrosis, a translational gap remains between the identification of putative antifibrotic targets and conversion of this knowledge into effective treatments in humans"

Samar A Antar et al 2023 written

"Most chronic inflammatory illnesses CII include fibrosis as a pathogenic characteristic. Extracellular matrix EM components build up in excess to cause fibrosis or scarring. The fibrotic proces FP s finally results in organ malfunction and death if it is severely progressive. Fibrosis affects nearly all tissues of the body. The fibrosis process is associated with chronic inflammation CI, metabolic homeostasis, and transforming growth factor-β1 signaling, where the balance between the oxidant and antioxidant systems appears to be a key modulator in managing these processes. Organ like the lungs, heart, kidney, liver, can be affected by fibrosis, whit an excessive accumulation of connective tissue CT. Organ malfunction is frequently caused by fibrotic tissue remodeling, which is also frequently linked to high morbidity and mortality. Long believed to be persistently progressing and irreversible, fibrosis has now been revealed to be a very dynamic process by preclinical models and clinical studies in a variety of organ systems.

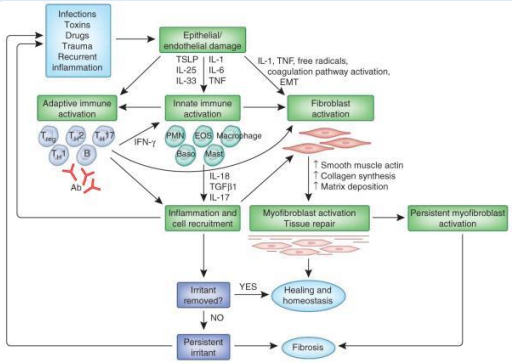

Figure n 1: Fromt.A. Wynn et al wound repair and fibrosis. Epithelial and/or endothelial damage caused by various insults triggers complex interconnected wound-healing programs to quickly restore homeostasis. The coagulation pathway, which functions to stem blood loss, is triggered first, followed by acute inflammation / activation of innate immune mediators like as resident macrophages, neutrophils, dendritic cells. Epithelial and innate immune cell–derived cytokines subsequently influence the activation of the adaptive immune response. The tissue damage can directly activate the adaptive immune response. Inflammatory / immune mediators (cytokines, chemokines, free radicals) attempt to eliminate the inciting factor while activating the resident quiescent fibroblasts into myofibroblasts that orchestrate angiogenesis and production of ECM components. Failure to adequately contain or eliminate the inciting factors can exacerbate the inflammatory response and lead to a chronic wound-healing response, with continued tissue damage, repair and regeneration, resulting in fibrosis.

Ziv Paz et al 2010

"Fibrosis is a pathological process that includes scar formation and overproduction of extracellular matrix by the connective tissue as a response to tissue damage. Today, we know more about the molecular mechanism that leads to fibrosis involving different type of cells, cytokines, chemokines, and tissue enzymes. Fibrosis was considered an irreversible process, at least clinically, and is still usually treated by anti-inflammatory and immunosuppressive agents. No proven antifibrotic therapy has shown efficacy in ameliorating the clinical course of fibrotic diseases FD, but our current understanding led to the development of different drugs with promising results, like: mycophenolate mofetil, interferon, relaxin, and IV immunoglobulin."

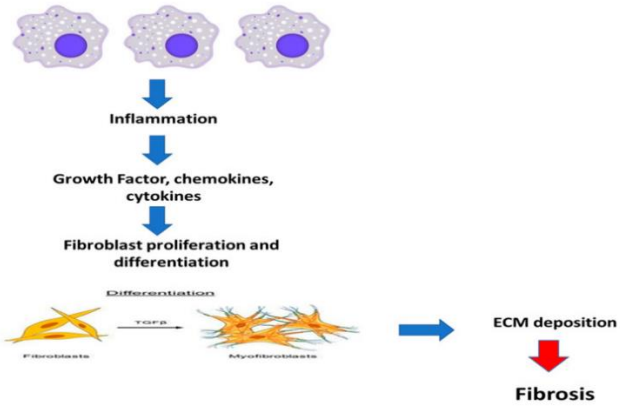

Figure n 2: The schematic diagram illustrates how fibrosis is triggered by persistent inflammation. TFG-β; transforming growth factor. From S.A. Antar et al.

A. Pellicoro et al 2012

"Liver fibrosis, and its end stage cirrhosis are a major cause of morbidity and mortality and therapeutic options are limited. The traditional view of liver disease as an irreversible process is obsolete and it is now evident that the development of liver fibrosis is a dynamic and potentially bidirectional process. Spontaneous resolution of scarring is seen in animal models of liver fibrosis and in human trials in which the stimuli responsible for chronic or repeated hepatic inflammation is successfully removed.

Key players in the process are hepatic stellate cells, macrophages, MMPs and their inhibitors Timps. It is evident that in advanced fibrotic liver disease AFLD, specific histological features define what is currently described as "irreversible" fibrosis. This includes the development of paucicellular scars enriched in extensively cross-linked matrix components, such as fibrillar collagen and elastin. Our work has focused on the role of macrophage metalloelastase in the turnover of elastin in reversible and irreversible models of fibrosis. We have shown that elastin turnover in liver injury and fibrosis is regulated by macrophages via Mmp-12 expression, activity and ratio to its inhibitor Timp-1. Failure of elastin degradation, together with increased deposition leads to accumulation of elastin in the fibrotic scars."

Qing Yang Yu et al 2022

"Pulmonary fibrosis PF, a terminal pathological change in the lung, is caused by aberrant wound healing, deposition of extracellular matrix, and eventually replacement of lung parenchyma by ECM. Pulmonary fibrosis induced by acute lung injury and some diseases is reversible under treatment. While idiopathic pulmonary fibrosis is persistent and irreversible even after treatment. The known factors associated with the development of irreversible fibrosis include apoptosis resistance of (myo)fibroblasts, dysfunction of pulmonary vessel, cell mitochondria and autophagy, aberrant epithelia hyperplasia and lipid metabolism disorder."

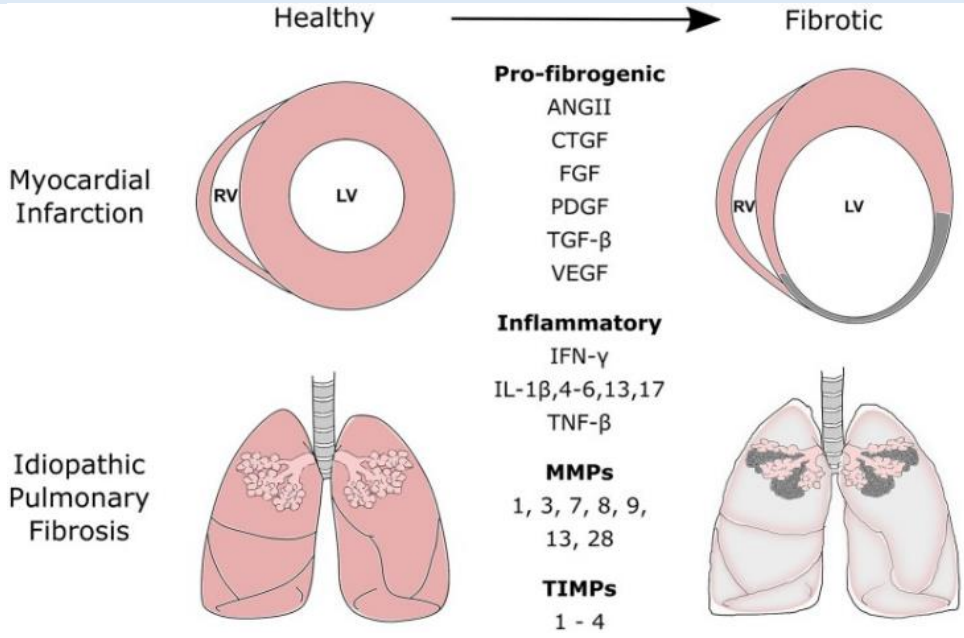

Figure n 3: from L.A Murtha et al Commonly secreted pro-fibrogenic growth factors, inflammatory proteins, matrix metalloproteinases, and tissue inhibitors of metalloproteinases during the fibrotic processes of myocardial infarction and idiopathic pulmonary fibrosis. Fibrotic disease is the result of a range of cellular and molecular responses activated by tissue injury. The fibrotic process is tightly regulated and involves phases: the inflammatory, proliferative, maturation phase. During the inflammatory and proliferative phases, a number of pro-fibrogenic, and inflammatory mediators are released to recruit and activate reparative mesenchymal cells like fibroblasts / myofibroblasts. These aid scar formation and maintains the structural integrity of the tissue. MMPs and TIMPs are released by fibroblasts. Their release can be mediated by chemokines, cytokines, growth factors released during the remodeling process. MMPs and TIMPs work to control the remodeling and degradation of extracellular matrix proteins at the site of injury.

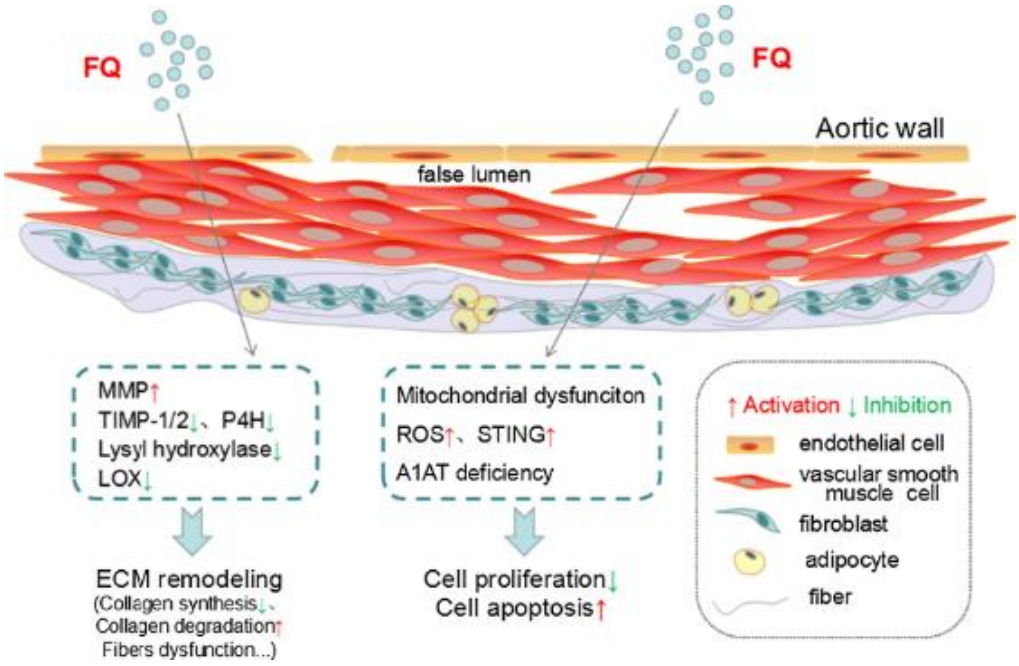

Figure n 4: From C Jun et al Mechanisms of FQ-induced AAD. FQ induces ECM remodeling via promoting MMP activation and inhibiting TIMP-1/2, P4H, Lysyl hydroxylase and LOX. FQ decreases cell proliferation and increases cell apoptosis through promoting mitochondrial dysfunction, ROS production, activation of STING. Patients with A1AT deficiency may associated with FQ-induced AAD. FQ fluoroquinolones, MMP martix metalloprotein, tissue inhibitors of matrix metalloproteinase, P4H prolyl 4-hydroxylase, LOX lysyl oxidase, ROS reactive oxygen species, STING stimulator of interferon genes, alpha-1 antitrypsin, ECM extracellular matrix, aortic aneurysm and dissection

According C. JUN et al

"Besides their typical antibacterial activity, FQ also exhibited diverse atypical biological profiles, like anti-Alzheimer activities, anti-tumor, anti-malarial and anti-tubercular"

Mechanisms of Action Research highlights the following primary mechanisms:

1. Downregulation of Dnmt1: Ciprofloxacin reduces levels of DNA methyltransferase 1 (Dnmt1), reversing hypermethylation defects that contribute to fibrosis.
2. Upregulation of Fli1: The drug increases the expression of Friend leukemia integration 1 (Fli1), an important transcriptional repressor of collagen.
3. MMP1 Activation: It induces the expression of matrix metalloproteinase 1 (MMP1), a collagen-degrading enzyme, utilizing an Erk1/2-dependent signaling pathway: Ciprofloxacin upregulates MMP1 by inducing Erk1/2 phosphorylation. Connective Tissue Deposition
4. MMP-9 Suppression: Fluoroquinolones have been shown to specifically abrogate transforming growth factor-beta (TGF-β) and PMA-induced Matrix Metalloproteinase-9 (MMP-9) production and activity. This inhibits pathological cell migration and extracellular matrix remodeling. Ciprofloxacin exerts paradoxical, tissue-dependent effects on Matrix Metalloproteinase-9 (MMP-9). It has been shown to downregulate MMP-9 in certain cancer cells (inhibiting migration), yet upregulate MMP-9 in connective tissues (contributing to tendon injury and aortic aneurysms)
5. Upregulation of Collagen Repressors: Studies on related fluoroquinolones (like ciprofloxacin) show antifibrotic effects in human scleroderma fibroblasts by increasing Friend Leukemia Integration Factor 1 (Fli1), a transcriptional repressor of collagen. Collagen Reduction: Studies show ciprofloxacin can significantly decrease Type I collagen mRNA and protein synthesis.
6. Connective Tissue Growth Factor Reduction: It significantly decreases the expression of CCN2/Connective Tissue Growth Factor (CTGF), a primary driver of tissue hardening.

And about the Metabolite Conversion: In mammals, enrofloxacin is partially metabolized into ciprofloxacin, which is the primary driver of its extracellular matrix and connective tissue effects.

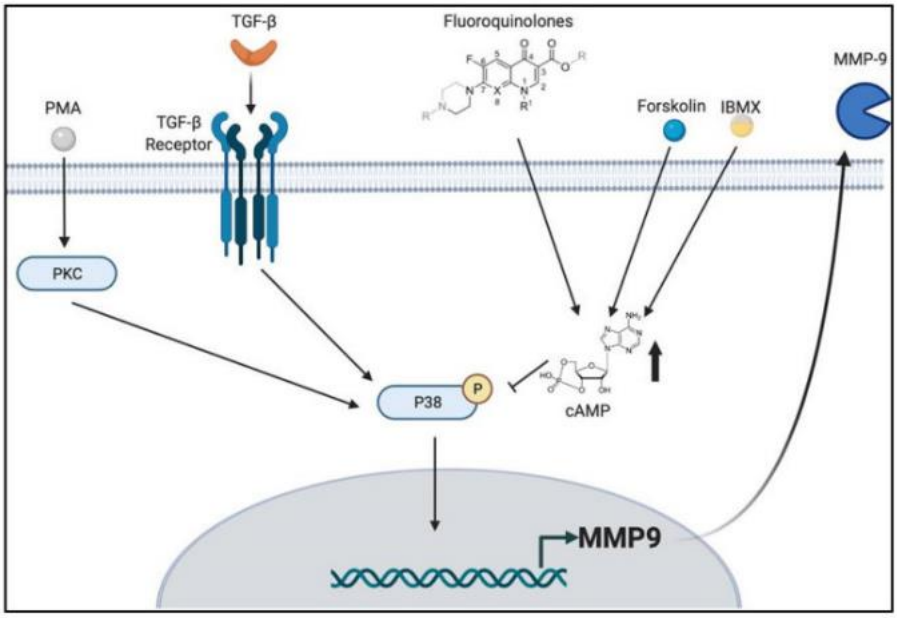

Figure n. 5: From C.Y. Huang et al The model by which fluoroquinolones (FQs) inhibit matrix metalloproteinase-9 (MMP-9) production by modulating p38 and cAMP signaling. In epithelial cells, TGF-β promotes invasion and metastasis by stimulating the p38-mediated signaling cascade in concert with canonical TGF-β signaling mediated by TGF-β receptor I and TβR-II. It has been recognized that FQs exert their anti-inflammation by producing intracellular cAMP, we discovered that FQs antagonize TGF-β and phorbol 12-myristate 13-acetate (PMA)-induced MMP-9 production by suppressing phosphorylation of p38 via cAMP production or via their components.

Material and methods

Whit an observational point of vew various research article are reported and then analyzed related the topic under investigation.

Various figure reported help in the general meaning. An experimental case report is submitted After all this a global conculsion is provided for future study.

Results :

From literature

Letitia Wong et al

"Uropathogenic E. coli 1677 was instilled transurethrally into adult C3H/HeOuJ male mice to induce chronic prostatic inflammation CPI. Collagen was labeled whit 3 H-proline administration for 28 days post-inoculation and 3 H-hydroxyproline incorporation measured to determine stability of the newly synthesized collagen. Inflammation score was evaluated- graded using a previously established system and total collagen content TCC was measured by picrosirius red staining quantitation and hydroxyproline content. Resolution of inflammation and reversal of collagen deposition CD was assessed after treatment with antibiotic enrofloxacin for 2 weeks on day 28 post-inoculation followed by an 8-week recovery period.

Decay analysis of incorporated 3H-hydroxyproline revealed the half-life of newly synthesized collagen to be significantly shorter in infected/inflamed prostates than in controls. Treatment with enrofloxacin completely eradicated the bacterial infection and allowed resolution of the inflammation. This was followed by marked attenuation of collagen content and correlation analysis verified a positive (+) association between the resolution of inflammation and the reversal of collagen deposition. Our findings show that inflammation-induced prostatic fibrosis IIPF is at least partly reversible and suggest that fibrosis of the human prostate may be addressed therapeutically by removing the cause of the inflammation or suppressing the inflammatory response" [1].

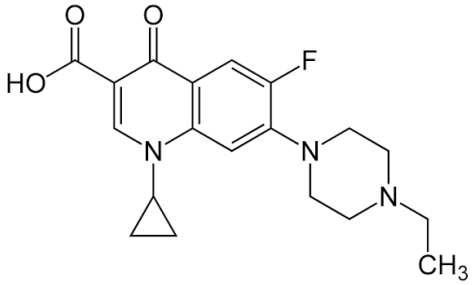

Figure. n 6: Enrofloxacin

A.M . Bujor et al

"We demonstrated that the CIP has dual antifibrotic effects on SSc dermal and lung fibroblasts by upregulating MMP1 and downregulating CCN2 and collagen type I levels.

Tendinopathies (tendon ruptures), rare but severe complications of CIP treatment. The pathologic mechanism is poorly understood, various mechanisms were proposed: the upregulation of matrix metalloproteinases followed by type I collagen degradation, inhibition of cell proliferation by the downregulation of cyclin B and cyclin-dependent kinase 1 and the inhibition of the tenocyte migration by the downregulation of focal adhesion kinase phosphorylation.

CIP-induced collagen downregulation DR in tendon cells is the result of increased ECM degradation due to the upregulation UR of various MMPs. Fibrosis in SSc is the result of the uncontrolled deposition of ECM that is presumably due to increased synthesis and to decreased degradation of matricellular components MC. CIP may affect SSc fibrosis trought regulating the aberrant expression of MMPs, leading to increased collagen turnover. MMP1 is the only enzyme capable of initiating the breakdown of interstitial collagens IC, including collagen type I, literature indicates that this enzyme is downregulated DR in SSc cells. Our study work demonstrates that, in addition to effects on MMP1, CIP treatment may directly block collagen synthesis in SSc fibroblasts, but not in healthy controls, by upregulating Fli1 levels" [2].

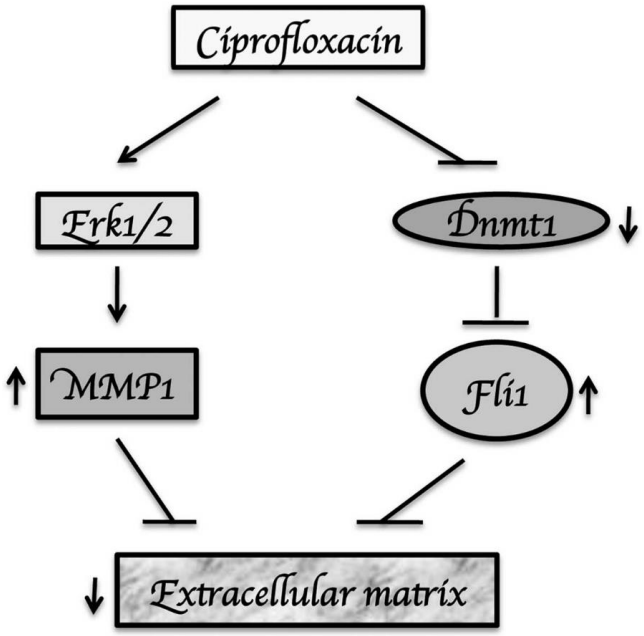

Figure n 7: form Bujor et al Schematic diagram showing the proposed mechanism of action for the antifibrotic effects of ciprofloxacin.

S. A. LeMaire et al 2020

"CIP treatment in WT Fbn1þ/þ mice reduced the level of LOX, a protein critical for cross-linking and stabilizing elastin and collagen" [3].

Enríquez-Casillas Rubén et al

"Scleroderma is an autoimmune connective AC tissue disorder that is characterized by microvascular injury, excessive fibrosis of the skin, and distinctive visceral changes that can involve the lungs, heart, kidneys and GI. Our results suggest that the administration OS of CIP for 6 months reduces the severity of symptoms affecting the skin of patients with systemic scleroderma SS, and does so without important secondary effects" [4].

Hannah Blau et al

"Both MXF and CIP are fluoroquinolones, possessing a cyclopropyl moiety at the position N1 of the quinolone core structure, appears to be associated with their immunomodulatory effects compared with other quinolones. MXF possesses a -CHO group on carbon 8 and a bulky C7 side chain, which differentiate it chemically from other fluoroquinolones, including CIP, and may be associated with MXF's wider antibacterial spectrum as well as increased tissue penetrance. These structural features and the higher concentration of MXF compared with CIP within cells may explain the enhanced immunomodulation by MXF shown in this study.

New therapies that downregulate DR the massive neutrophilic inflammation within CF airways as well as other inflammatory lung diseases ILD are urgently needed. Therapeutic targeting of the production of IL-8, IL-6, and other inflammatory proteins may most effectively be achieved by inhibiting

key intracellular signaling molecules. Our work demonstrates that MXF, and to some extent CIP, function in this way and might be new modalities to prevent progressive destruction of lung parenchyma in these diseases "[5].

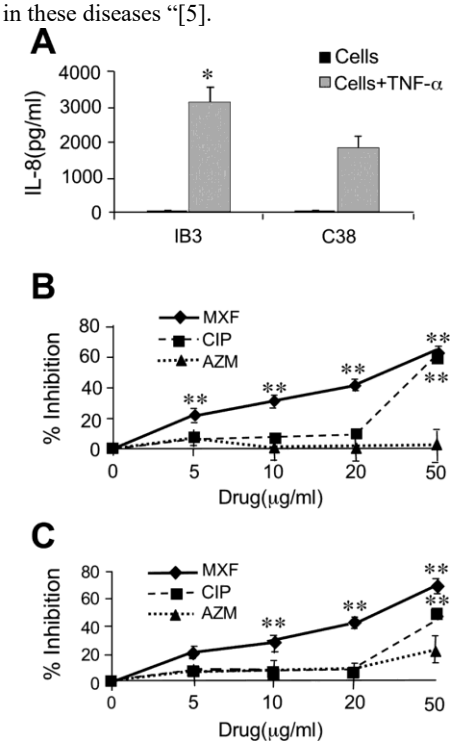

Figure n 8: from H Blau et al IL-8 secretion by IB3 [a cystic fibrosis (CF) bronchial cell line] and C38 cells stimulated with TNF-α. A: effect of TNF-α stimulation. IL-8 secretion by IB3 and C38 cells cultured in Lab. of Human Carcinogenesis basal medium #8 (LHC-8), serum-starved for 24 h, and incubated with 50 ng/ml TNF-α for a further 48 h. Results are expressed as means ± SE of 8 experiments performed in duplicate. *P < 0.001, TNF-α-stimulated IB3 cells vs. C38 cells. B and C: effect of drugs on IL-8 secretion. IB3 (B) and C38 (C) cells were incubated with TNF-α together with 5–50 μg/ml MXF, CIP , or AZM for 48 h, and % inhibition of IL-8 secretion was determined by ELISA. Results are expressed as means ± SE of 3 experiments performed in duplicate. **P < 0.05, cells treated with TNF-α and drugs vs. TNF-α-stimulated cells.

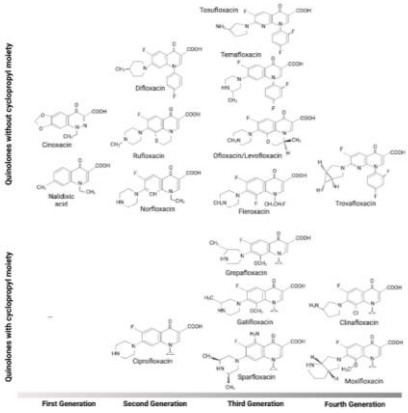

Figure n 9: from Resti Yudhawati et al Structure of fluoroquinolones with and without cyclopropyl moiety.

J H Yoon et al

"The use of FQs is not without risk: Tendonitis and spontaneous tendon rupture have been reported. We have studied the effects of enrofloxacin, used in domestic animals, on tendon cell cultures established from equine superficial digital flexor tendons. Effects on cell proliferation and morphology were studied using cell counting and scanning electron microscopy. Monosaccharide content and composition was determined by CG – MS analysis. Western and Northern blot were utilized to evaluate the synthesis and expression of 2 proteoglycans, biglycan and decorin. Our data demonstrate that enrofloxacin inhibits the cell proliferation, induces morphological changes, decreases total monosaccharide content and alters small proteoglycan synthesis at the glycosylation level in equine tendon cell cultures. These effects are more pronounced in the juvenile tendon cells than in adult equine tendon cells. We hypothesize that morphological changes and inhibition of cell proliferation are a result of impaired production of biglycan and decorin, proteoglycans involved in fibrillogenesis of collagen, the most important structural component of the tendon of enrofloxacin-treated tendon cells" [6].

Kaveh Khazaeel et al,

"Enrofloxacin increases apoptosis in chondrocytes and decreases their numbers. Enrofloxacin use in growing lambs even at recommended

therapeutic dose is not completely safe on articular cartilage. Higher doses of enrofloxacin induce severe changes in lamb articular cartilage" [7].

Diva Baggio et al

Current fluoroquinolone use* and the hazard of collagen-associated adverse events

Antibiotic exposure outcome event	Unadjusted HR	95% CI	Adjusted† HR	95% CI
Fluoroquinolones				
Tendon rupture	3.13	2.98 to 3.28	2.40	2.24 to 2.57
Retinal detachment	1.28	0.99 to 1.65	1.47	1.08 to 2.00
Aortic aneurysm	2.72	2.53 to 2.93	2.24	2.02 to 2.49
Amoxicillin (negative tracer)				
Tendon rupture	1.56	1.46 to 1.66	1.41	1.29 to 1.54
Retinal detachment	1.44	1.14 to 1.81	1.47	1.08 to 2.00
Aortic aneurysm	1.74	1.59 to 1.90	1.50	1.32 to 1.70

*Patients considered exposed during fluoroquinolone course and for 30 days following treatment.
†Adjusted for baseline characteristics including sex, income quintile, prior hospital admissions, prior physician visits, diabetes mellitus, hypertension, atherosclerosis, chronic kidney disease, chronic obstructive pulmonary disease, hypothyroidism, depression, inflammatory bowel disease, malignancy, liver disease, prior pneumonia, prior urinary tract infection.

Figure n. 10: From D. Daneman et al 2015

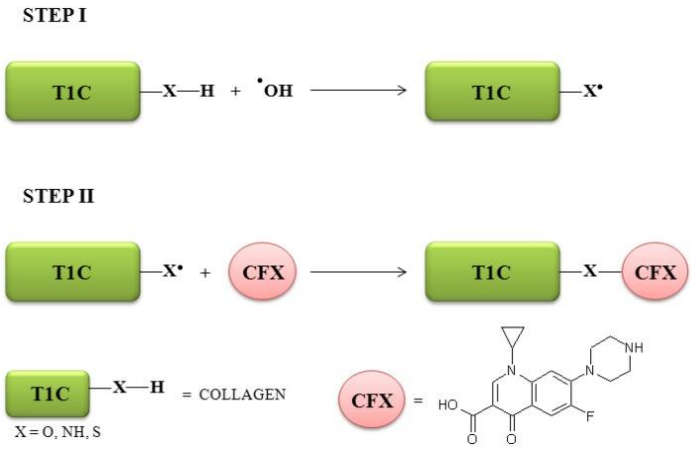

Figure n. 11: from F Puoci et al 2012 Insertion of CFX into collagen chain. The covalent incorporation of CFX into collagen chains was confirmed by performing FT-IR and UV-Vis analyses and the amount of CFX bound per gram of polymeric conjugate was 25 mg.

Yuki Enoki et al

"A similar inhibition in a H2O2/UV system and PMA-stimulated neutrophils was observed in the case of LVFX, indicating that LVFX is capable of scavenging OH radicals" [9].

Jun, C., Fang, B.

"Matok et al. revealed that there was a significant association between FQ exposure and an increased risk of arrhythmia (85% increase) and CV (71% increase). In 2018, FDA issued several "black box warnings" against FQ with the latest safety announcement warning about an increased risk of ruptures in the aorta blood vessel in certain patients. FQ may interfere with ECM integrity in the aortas. Dysregulation of ECM homeostasis disrupted ECM integrity and impaired biomechanical strength, which finally triggered progressive aortic weakening, dissection, or rupture. According to studies, enzymatic degradation of ECM by MMPs and vascular remodeling constituted the most prominent characters of AA. TIMPs may inhibit the development of AA. Evidence confirmed that FQ reduced collagen production in tenocytes and fibroblasts. Researches showed that CIP suppressed TIMP-1 expression but enhanced MMP expression in the cornea, in tendon cells and tissues, in fibroblasts, which finally promoted MMP activation and tissue destruction. It was suggested that CIP greatly up-regulated MMP activity more than twofold in cultured human aortic smooth muscle cells. Human aortic fibroblasts exposed to FQ showed an increased capacity for ECM dysregulation by reducing the expression of collagen and endogenous protease inhibitors protein. They demonstrated collagen degradation and decreased TIMPs activity in human aortic fibroblasts cultured with 2 days FQ. A recent study confirmed that CIP significantly increased the incidence of AAD (79%) in mice. Specifically, in the mouse model of AAD that CIP exposure reduced the expression of LOX, a critical enzyme in the assembly and stabilization of elastic fibers and collagen.CIP us enhanced MMP expression and activity as well as elastic fiber fragmentation in the aortas. In cultured smooth muscle cells, CIP markedly down-regulated LOX levels and activity while up-regulated MMP levels. FQ is considered to be powerful iron chelators. Prolyl 4-hydroxylase and lysyl hydroxylase are iron-dependent enzymes, which play central roles in the post-translational modification of collagen. These enzymes promote collagen maturation through hydroxylation of proline and lysine residues to induce collagen cross-linking, which is essential for the tensile strength of collagen fibers. Badal et al. The effect of FQ on the inhibition of cell proliferation and induction of cell apoptosis may lead to aortic destruction. Evidence showed that FQ inhibited cell proliferation in various cells, including tenocytes, osteoblasts and chondrocytes, and induced cell apoptosis in various cells, like tenocytes and lens epithelial cells. Mechanically, as a DNA topoisomerase inhibitor, CIP induced nuclear and mitochondrial DNA damage and the the release of DNA, which finally promoted mitochondrial dysfunction, reactive oxygen species production, activation of stimulator of interferon genes, the cytosolic DNA sensor and cell death "[10].

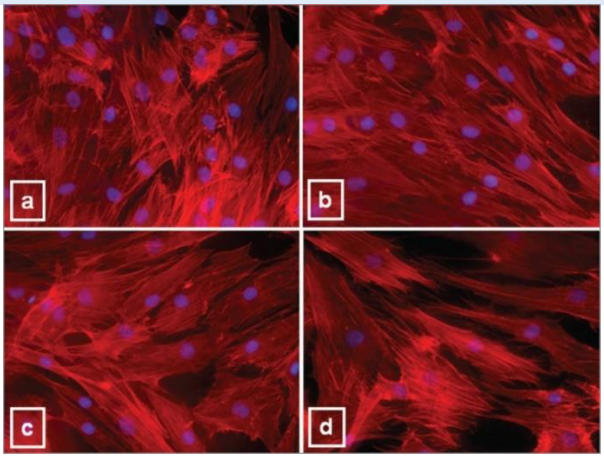

Figure n: 12: from A. Menon et al 2013 Immunofluorescence analysis of the actin cytoskeleton in tenocytes untreated and treated with CPX. Representative immunofluorescence photomicrographs of microfilament distribution, evidenced by rhodamine-phalloidin labeling, in CT (a) and tenocytes after 10 μg/ml (b), 20 μg/ml (c) and 50 μg/ml CPX (d). DAPI was used for nuclear staining. Original magnification: 40×.

Aura Rusu et al

"Underlying Mechanisms of Aortic Aneurysm and Aortic Dissection The mechanism of FQ-induced ruptures or tears in the aorta blood vessel remains to be clarified. One proposed mechanism claim that FQs upregulate cell matrix metalloproteinases. Consequently, collagen fibrils (types I and III) will be reduced. FQs may interfere with extracellular matrix (collagen and elastic fibers) integrity in the aortas. Disrupted extracellular matrix integrity correlated with impaired biomechanical strength triggers progressive aortic degradation until dissection or rupture. It was reported that FQs decrease collagen production in mouse tympanic membrane fibroblasts (CIP) and tenocytes (human-derived tendon cells). Many studies have shown that CIP enhanced MMPs expression, which mediates collagen and elastic fiber degradation. CIP was associated with collagen degradation and decreased the inhibitors of the matrix metalloproteins expression" [11].

Bakhtin V.M. et al

"The complexing activity of levofloxacin and moxifloxacin was similar to that of EDTA and was greater than that of citrate ionsand glycine. FQ may compete with bioorganic ligands for magnesium ions. High complexing activity of FQ may lead to serious adverse reactions caused by intracellular Mg2+ deficiency" [12].

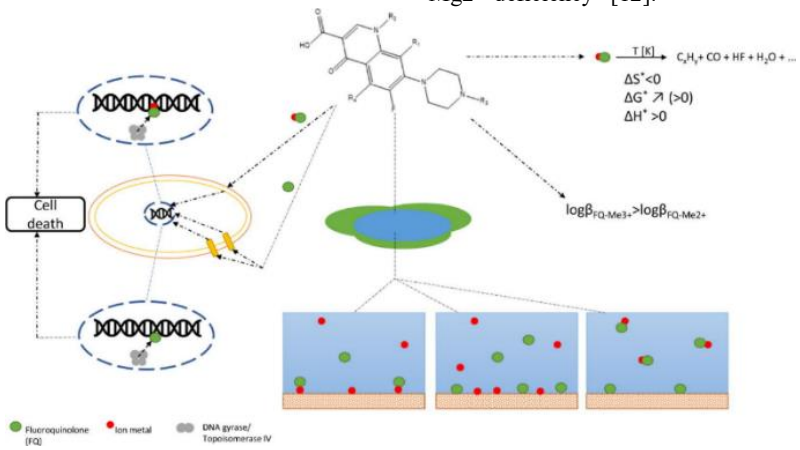

Figure n. 13: Form Agnieszka Cuprys et al 2018 Fluoroquinolones metal complexation and its environmental impacts.

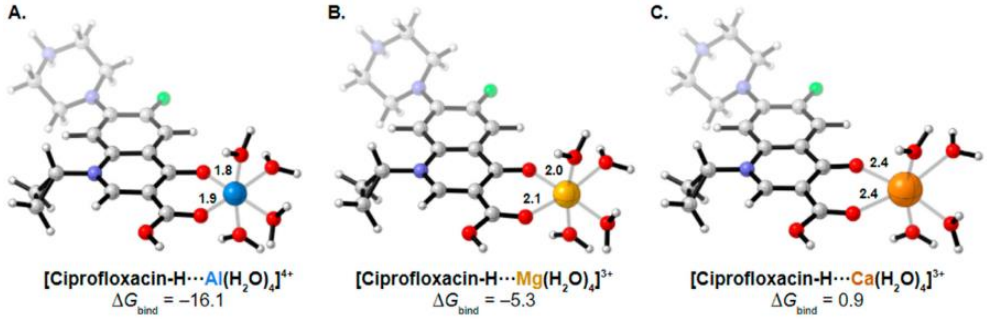

Figure. n 14: From D.M Walden. Computed structures and predicted free energies of binding (ΔGbind) between N-protonated cationic CIP and (A) aluminum hydrate, (B) magnesium hydrate, and (C) calcium hydrate. Structural images generated using CYLView.

Experimental hypotesys part

Two group of patients with hystory of chronic prostatitis and documented reduced urinary flux: 20 patients group A nd 20 in the gruop B. Before to start this test, it must to be measured the all patient basal urofluxometry. The group A must to be treated with ciprofloxacin for 15 days at usual posology. Gre group B must to be treated with Suslfametoxazole and trimetoprimfor 15 days at usual posology. To all of this patient must to be added oral antinflamatory therapy. After this period must to be tested all patient with uorofluxometry. If increased flux in the group A this can suggest more efficacy in reverse the Bladder neck- urethra fibrosis related the chronic prostatitis. (hypotesis).

Discussion

In medicine hystory the fibrotic process was considered as irreversible with many implications in various severe condition affecting also relevant organs. The fibrotic process if in acute seem reversible in chronic phases it can become more irreversible. Various flurochinolon show in literature efficacy in reverse some fibrotic process with deposition of connective tissue. Betwen the MOA there is a reduction of infalmatory process linked to infection.

The MOA of the fluorochinolon in reverse the fibrotic process imply modify in various moleculas signal systems.

1)Downregulation of Dnmt1, 2) Upregulation of Fli1, 3) MMP1 Activation, 4) MMP-9 Suppression. Ciprofloxacin exerts paradoxical, tissue-dependent effects on Matrix Metalloproteinase-9 (MMP-9). It has been shown to downregulate MMP-9 in certain cancer cells (inhibiting migration), yet upregulate MMP-9 in connective tissues (contributing to tendon injury and aortic aneurysms) 5) Upregulation of Collagen Repressors, 6) Connective Tissue Growth Factor Reduction 7) ions ecomplexing activity

“Besides their typical antibacterial activity, FQ also exhibited diverse atypical biological profiles, like anti-Alzheimer activities, anti-tumor, anti-malarial and anti-tubercular” See C. Jun et al Of great interest the efficacy in Influenza Virus-Induced Lung Injury [9] so not only antibacteric effect.

In literature it is clear the florochinolon show a toxic class effect. [9] and this ADR can be a driver to address the reseach: tendom rupture, aorta rupture. In oral therapy is wwll knowed the risk of serious tendinopaty since also rupture. (Achilles tendon) Fundamental in this filed are the animal model, and preclinical studies even if the clinical trial can be the right instrument to verify the efficacy in humans as antifibrotic molecule.

Conclusion

After seeing all reported it is crucial to verify if the class effect in reverse fibrotic process is related only to the antibacterial properites that contribute to reduce local infections or there is another mechanism of action not related to the antimicrobial effect.

Tha fact that the fibrotic process was hystorically considered as irreversible make this article interesting to continue the research in this field. Finally, because this effects in some fibtoric processi is is needed to label these drugs like Some fluorochinolon as antifibrotic? It is so recomended to perform clinical trial for evaluate this new condition a part from the In vitro sudy or in animal model.

Conflict of interest: No.

Ethical consideration: all international ethical rules were followed in this work.

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