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VIEWPOINT

Fluoroquinolones are a potent form of chemotherapy

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Fluoroquinolones (sometimes referred to as quinolones) are generally considered the most effective and useful of all the topical ocular antibiotics. With emerging antibiotic resistance becoming an increasing global problem, eye-care providers are told to use these agents judiciously and only for the most severe ocular infections. However, there are additional reasons to limit the use of these agents. There are increasing reports in America of serious adverse effects of these antibiotics particularly from systemic use (oral and intravenous).[1] In addition to the potentially serious health impacts there are also considerable economic implications,[2] and many hundreds of lawsuits against manufacturers in America both underway and settled.[3] As the side-effects are more likely with systemic dosing than topical application, eye-care providers may be unaware of these potential adverse effects. The extent of their effects, including immunomodulatory, pro-apoptotic, anti-proliferative and anti-metastatic actions, is highlighted by these agents being repurposed as anti-cancer agents.[4] The purpose of this viewpoint is to describe the unfortunate consequences that can occur in a portion of patients taking systemic fluoroquinolones, and to share the view that eye-care practitioners should consider them cytotoxic and potential anti-cancer treatments.

Quinolone is a generic term referring to a class of drugs that include quinines, naphthyridines, fluoroquinolones, quinazolines, and isothiazoloquinolones. The fluoroquinolones (a subset of the quinolones) are a group of broad spectra, bactericidal antibiotics with a similar mode of action that includes inhibiting the replication and transcription of bacterial DNA synthesis by blocking DNA gyrase or topoisomerase-IV.[5] They are commonly used to treat respiratory and urinary tract infections. In Australia ciprofloxacin, moxifloxacin, and norfloxacin are available for systemic use.[6] Australian clinicians, primarily doctors, must obtain authority to prescribe quinolones under the Pharmaceutical Benefits Scheme and can prescribe them only for specific infections.[6] The purpose of these restrictions has been to minimise bacterial resistance to this class of agents.[7] The *Australian Medicines Handbook* states 'Worldwide resistance to quinolones is increasing. Judicious use may extend their clinical life'. However, it is the serious adverse reactions that have majorly limited their use.

Eye-care providers are well aware of the ocular uses of the fluoroquinolones for bacterial corneal infections. In Australia only two second-generation agents, ofloxacin and ciprofloxacin, are available for ocular use.[6] In America this group includes ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin. Similarly, their use has been restricted to slow-emerging resistance. Again, serious adverse reactions are mentioned for the topical ocular agents but these are much less likely to occur than with systemic medications as the dose is so much lower (more than 1,500 eye drops equate to one 250 mg tablet). Precautions include if patients have a history of tendon damage or reported hypersensitivity to previous quinolone use.[6]

General side-effects of systemic agents

Eye-care providers should be aware of the possible side-effects from systemic use (Table 1). Although the adverse effects are stated to be uncommon or rare, many thousands of people are members of support groups on Facebook for affected individuals (for example, Fluoroquinolone Toxicity Group, Ciprofloxacin Toxicity Group), and there are many hundreds of posts on these sites every month. From 2013 to 2017 there was an average of 625 enquiries to the American Food and Drug Administration's (FDA) Division of Drug Information about systemic fluoroquinolones;[18] these were primarily from patients describing problematic long-term symptoms.

Side-effects of systemic agents include a serious and potentially permanent peripheral neuropathy.[3] The onset of symptoms (such as tingling, numbness or pain of the feet, legs, hands or arms) may be rapid, that is, within a few days of starting treatment.[19] Since 2004 this potential side effect has been listed on patient information sheets. In 2008, the FDA required another warning be added, alerting patients of the risk of tendon damage and rupture, which might be due to the release of tissue-damaging substances or enzymes that degrade collagen. This risk was updated in 2016 to indicate that these effects could be permanent. In 2018 risks of low blood sugar and mental health problems were added. It is suggested that fluoroquinolones use can increase the risk of suicidal behaviour.[20] Fluoroquinolones can also weaken the aortic wall presumably also by damaging collagenous proteins, increasing the risk of its dissection or aneurysm which are life-threatening events.[15] This large collection of irreversible effects has led to the description of a potentiality permanent syndrome called fluoroquinolone-associated disability (FQAD)[21] and a new verb of having been 'Floxed'.

Ocular side-effects of systemic agents

Collagen also serves as a critical component of the vitreous body of the eye and in maintaining retinal attachment, but whether fluoroquinolones mediate retinal detachment

Relative risk	Adverse effect	Evidence
Common > 1%	Allergy, rash, itch	Reviewed in McGee et al.[8]
	Nausea, vomiting, diarrhoea, abdominal pain, indigestion (dyspepsia)	Norrby;[9] Oliphant and Green[10]
Infrequent (0.1 to 1%)	Headache, dizziness	Norrby;[9] Oliphant and Green[10]
	Insomnia, depression	Norrby;[9] Oliphant and Green[10]
	Restlessness, tremors	Reviewed in Oliphant and Green[10]
	Sensory disturbance (hearing, taste, vision)	Oliphant and Green[10]
	Joint pain (arthralgia), muscle pain (myalgia)	Reviewed in Kim and Del Rosso[11]
	Tendinitis (inflamed tendons), arthritis (inflamed joints)	Norrby;[9] Kim and Del Rosso[11]
	Interstitial nephritis (kidney inflammation), high liver enzymes (this may indicate inflammation or damage to cells in the liver)	Norrby[9]
Rare (< 0.1%)	Anaphylaxis (potentially life-threatening, severe allergic reaction), angioedema (swelling of skin, tissue under the skin or mucous membranes), Stevens-Johnson syndrome (serious disorder of skin and mucous membrane), toxic epidermal necrolysis (extremely severe skin reaction)	Reviewed in McGee et al.;[8] Patel et al.[12]
	Peripheral neuropathy (nerve damage may be irreversible)	Morales et al.[13]
	Hypo- or hyperglycaemia, hepatitis (inflammation of the liver), blood dyscrasias (blood disorder), *Clostridium difficile*-associated disease (an infection of the colon caused by the bacteria *C. difficile*)	Reviewed in Deshpande et al.[14]
	Aortic aneurysm or dissection	Pasternak et al.[15]
	Tendon rupture, especially of the Achilles tendon (onset may be rapid or take months)	Oliphant and Green;[10] Wise et al.;[16] Stephenson et al.[17]

Table 1. Potential adverse effects from systemic use of fluoroquinolones

remains controversial. Daneman et al.[22] performed a longitudinal population-based study in Ontario, Canada with the aim to determine, in addition to other potential side-effects, whether there was an increased risk of retinal detachment in the group that had taken fluoroquinolones during the study period. They did not find a significant association and suggest a range of possible reasons, including that the study was underpowered, the type of collagen in retinal tissue (type II) may be less affected than other forms of collagen, or the retina is under less tension than the ankle tendons which are prone to rupture. Etminan et al.[23] had previously reported a link between current oral fluoroquinolones and increased risk of retinal detachment; they stated that the increased risk was small at only four per 10,000 person-years, although this was five times the usual risk.

Side-effects of topical ocular agents

It is generally considered that topical fluoroquinolones do not pose the same risk as systemic use,[6] are generally considered safe to use,[24] and do not appear to give rise to side-effects like arthritis or tendinitis, although topical agents may be problematic to the eye itself. Thompson[24] has provided a comprehensive review of the typical ocular side-effects (Table 2) which are dose-dependent. Toxic effects on ocular collagen may be the reason for the observed increased risk of corneal perforation, although the systematic review by McDonald et al.[27] on the use of topical antibiotics for bacterial keratitis did not find evidence of increased risk of corneal perforation with fluoroquinolones compared with other antibiotic combination therapies (usually aminoglycoside–cephalosporin).

Using animal models, it has been shown that topical quinolones increase the expression of inflammatory markers matrix metalloproteinase (MMP)-1, MMP-2, MMP-8 and MMP-9,[28] suggesting the potential for corneal cytotoxicity and impaired wound healing. Related to this, these agents are toxic to the corneal keratocytes and endothelial cells;[29] effect is maximum with ciprofloxacin, followed by ofloxacin, gatifloxacin and moxifloxacin and least with levofloxacin.

A new understanding of the effect on human mitochondria and cytotoxic capability

As described this class of antibiotics does not just harm microbes they can severely damage human cells too (as can other antibiotics). The key question is why, that is, how does the damage occur? The underlying cause appears to be the adverse effects on mitochondria which are similar in humans and bacteria; the mitochondria of human cells are thought to have evolved billions of years ago from bacteria-like cells.

Kalghatgi et al.[30] have reported that antibiotics build up reactive oxygen-containing molecules in mitochondria causing severe oxidative stress and preventing them from functioning normally. It has also been shown that ciprofloxacin causes DNA breaks in mitochondria in mammalian cell culture models.[31] The fluoroquinolones may also bind iron atoms from the active sites of enzymes that modify DNA, and this could lead to epigenetic changes that cause adverse effects.[32]

Michalak et al.[21] suggest a range of possible treatment avenues to investigate, some of which include: (a) reduction of the oxidative stress; (b) restoring the altered mitochondrion potential; (c) stimulating mitochondrial proliferation; and (d) regulating the disturbed gene expression and enzyme activity. Mitochondria-targeted antioxidants protect against mitochondrial damage and may be useful in preventing damage.[33] It is unknown whether taking a simple antioxidant like vitamin C in conjunction with antibiotic treatment might limit some of these effects, although some minerals (for example calcium, iron, magnesium, zinc) bind to these antibiotics and prevent their absorption.[10] There is no currently effective treatment to prevent these adverse effects.

Relative risk	Adverse effect	Evidence
Reasonably likely (> 10%)	Local irritation, burning, stinging and itching	Reviewed in Thompson[24] Hyndiuk et al.[25]
	Corneal precipitation	Hyndiuk et al.[25]
	Corneal perforation	Mallari et al.[26]
Common (> 1% to 10%)	Eyelid oedema and lid margin crusting	Hyndiuk et al.[25]
	Blurred vision	Reviewed in Thompson[24]
Infrequent (0.1 to 1%)	Chemosis	Hyndiuk et al.[25]
	Hyperaemia	Reviewed in Thompson[24]
Rare (< 1%)	Lacrimation	Hyndiuk et al.[25]
	Superficial punctate keratitis	Hyndiuk et al.[25]

Table 2. Ocular side-effects of topical fluoroquinolones

Repurposing as experimental anti-cancer treatments

The fluoroquinolones were developed as antimicrobial agents, but emerging data shows their potential to treat cancer. Paul et al.[34] conducted a meta-analysis of quinolone trials in cancer patients where the quinolone was administered prophylactically to reduce the risk of infection. A significant reduction in non-infection-related mortality was observed (relative risk ratio = 0.54) and they suggested this was compatible with an anti-cancer action of these agents. The researchers note that although the anti-infection action was taken into account in the analysis, some of the reduction in risk might still have been due to an anti-infection activity. Regardless, this data highlighted the positive effect of quinolones on the survival of cancer patients.

More recently, the potential for the fluoroquinolones to have therapeutic application as anti-cancer agents has been explored by Yadav and Talwar;[4] this is called drug repositioning or drug repurposing. The production of quinolone hybrids may lead to the development of agents with even greater anti-cancer activity.[35] These agents could be used in combination with other known anti-cancer drugs for an improved therapeutic effect (reviewed in Yadav and Talwar).[4]

There are numerous examples in the literature of the effects on cancer cell proliferation (reviewed in Idowu and Schweizer[36] and Yadav and Talwar[4]). Some key points and examples include the following (Table 3). It has been found that moxifloxacin and ciprofloxacin supress the proliferation of pancreatic cancer cell lines.[41] There is evidence that ciprofloxacin inhibits cell growth and intrinsic apoptosis activities of cancer cells.[37] There are data showing that several novel fluoroquinolones display anti-cancer properties against human breast cancer (MCF-7) and non-small-cell lung cancer lines (A549).[38]

It has been proposed that these effects are due to immunomodulatory, pro-apoptotic, anti-proliferative and anti-metastatic actions (Figure 1).[4] Complicated cellular effects are involved including blocking the S-phase of the cell cycle, decrease in the levels of p27, p21, CDK2, cyclin-A and cyclin-E, triggering of extrinsic and intrinsic mitochondrial apoptotic pathways, down-regulation of anti-apoptotic protein Bcl-xL and upregulation of pro-apoptotic protein Bak.[4] Thus, although the effect on mitochondria may account for FQAD, this action is also likely involved in the observed anti-cancer activity.

Viewpoint summary

The fluoroquinolones do have actions against human cells, that is, they have more than just antibacterial activity. These actions account for the adverse reactions observed with these agents but also mean these

Observation	Model	Evidence (reviewed in Yadav and Talwar[4])
Inhibit cell growth, apoptosis	Colon cancer cells	Herold et al.[37]
Meta-analysis shows reduced mortality rate in cancer patients	Humans with cancer	Paul et al.[34]
Anti-cancer effects	Human breast cancer cell lines, non-small-cell lung cancer cell lines	Al-Trawneh et al.[38]
Anti-cancer action potentiation of other agents	Prostate cancer cells	Pinto et al.[39]
Extracellular signal-regulated kinase-mediated apoptosis	Human colon cancer cells	Jemel-Oualha et al.[40]
S-phase arrest, apoptosis	Human pancreatic cancer cells	Yadav et al.[41]

Table 3. Selected evidence of anti-cancer action

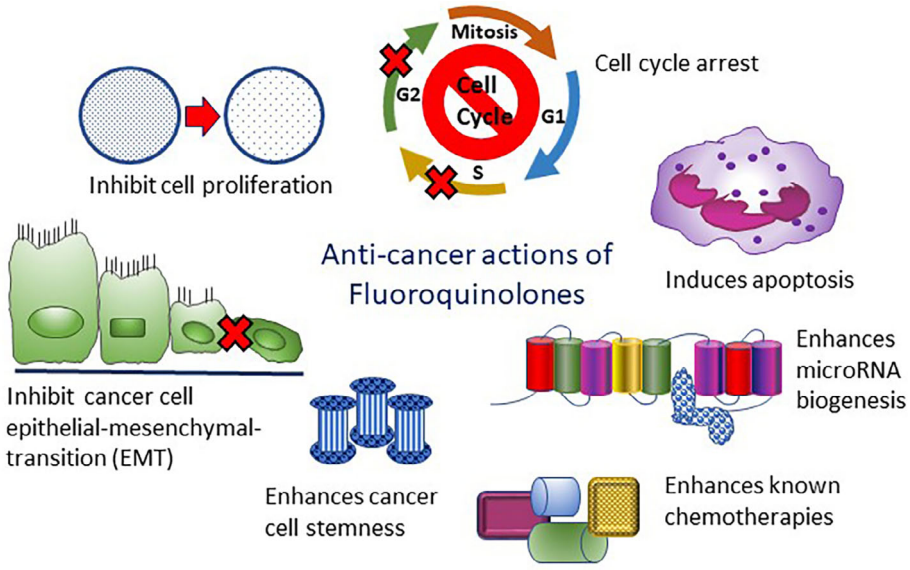

Figure 1. Suggested anti-cancer activities of the fluoroquinolones. These include inhibition of cell cycle, cell proliferation and inhibition of epithelial–mesenchymal transition. Enhancing the stemness (original cell character) of cancer cells, ability to induce cell apoptosis and microRNA biogenesis. They can also enhance the anti-cancer effect of other known chemotherapies. Figure based on Yadav and Talwar.[4]

agents have the potential to be repurposed as anti-cancer therapies. Patients taking these agents should read the warning on the packaging. They need to be aware of the potential risks and to seek care immediately if they experience symptoms like numbness, weakness, tingling, burning or pain. Patients using ocular forms should be monitored for corneal thinning and risk of corneal perforation.

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