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A Commentary on "Suppressive Effect of Topical Moxifloxacin on Imiquimod-Induced Model of Psoriasis in Mice"

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Commentary

The *Journal of Experimental Neurology* frequently highlights studies that bridge the gap between neurological disorders and systemic conditions, particularly those with an immunological component. The recent article, "Suppressive Effect of Topical Moxifloxacin on Imiquimod-Induced Model of Psoriasis in Mice," by Abbas *et al.*, presents intriguing data suggesting a potential role for the fluoroquinolone antibiotic moxifloxacin in the treatment of psoriasis, a chronic inflammatory skin disorder. While seemingly outside the direct purview of neurology, this study raises important questions about neuro-immune interactions in inflammatory diseases and the potential for repurposed drugs to impact neurological health.

Psoriasis is a common, chronic, and persistent skin disorder that is often hereditary. It is a disfiguring, recurrent, inflammatory, and proliferative illness that is increasingly recognized for its systemic effects, including associations with cardiovascular disease, metabolic syndrome, and even neuropsychiatric disorders [1]. Specifically, studies have shown a higher prevalence of depression, anxiety, and even cognitive impairment in individuals with psoriasis compared to the general population. Some research also suggests a potential link between psoriasis and an increased risk of developing neurological conditions such as multiple sclerosis and Parkinson's disease, although more research is needed to understand these relationships fully [2,3].

The underlying inflammation in psoriasis involves a complex interplay of immune cells and cytokines, some of which, $CD4^+$ T lymphocyte cell growth and proliferation into Th17 and Th1 cells, are supported by the generation of pro-inflammatory cytokines. Cytokines comprising IL-12, IL-23, and TNF-α have also been linked to psoriasis pathogenesis. The adaptive immune system needs to be triggered to sustain psoriatic inflammation maintenance. Th17 cells secrete cytokines, for example, IL-17, IL-21, and IL-22, which activate the JAK/STAT pathway and promote keratinocyte proliferation [4–6]. This stimulation phosphorylated and regulated pro-inflammatory gene transcription [7,8]. IL-17, TNF-α, and IFN-β increase keratinocyte development as well. The TNF-IL-23-Th17 inflammatory pathway is necessary for signaling pathways that contribute to psoriasis progression [9,10].

TNF-α and IL-17, are also implicated in neuroinflammation and neurodegenerative processes [11,12]. Understanding the mechanisms by which moxifloxacin modulates these inflammatory pathways in the skin could potentially offer insights into similar processes in the nervous system.

Fluoroquinolones are an advantageous class of antibiotics with universal adoption because of their extensive spectrum of antibacterial properties, broadened therapeutic index, and controllable resistance profiles. Researchers are still interested in fluoroquinolones owing to their diversified range of unforeseen biological consequences, involving immune-modulatory, anti-oxidative, antimitotic, and anti-inflammatory actions, as well as suppression of cytokines, chemokines, and reactive oxygen species [13].

Fluoroquinolones exert their immune-modulating properties by preventing the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-17, IL-6, and IL-8, while also demonstrating anti-oxidative capabilities through inhibiting oxidative markers such as MPO and MDA [14].

These medications impeded the proliferation of inflammatory Th17 lymphocytes and suppressed L-17 production. The anti-inflammatory activity of fluoroquinolones may be correlated with blocking PDE and enhancing intracellular cAMP concentrations [15]. Plus, it has been documented that certain fluoroquinolones possess anti-proliferative abilities *in vitro* by initiating apoptosis, interfering with the metabolic transformation of malignant cells, boosting the absorption of different chemotherapy-related medications, and/or modulating immune responses [14].

Moxifloxacin suppresses the production of pro-inflammatory cytokines among human monocytes, both *in vitro* and *in vivo*, in laboratory animal models of inflammation [16].

Moreover, moxifloxacin exhibits anti-inflammatory actions on human airway epithelial cells by dramatically downregulating the secretion of IL-8 and GM-CSF cytokines, both in the presence and absence of TNF-α activation [17]. Another study found that moxifloxacin reduced inflammation by inhibiting LPS-triggered elevation of TLR4, NF-κB p65, TNFα, and IL-6 transcription levels in mouse macrophages [16].

The study by Abbas *et al.* utilizes the imiquimod-induced psoriasis model in mice, a widely used tool to mimic the inflammatory and proliferative features of human psoriasis. The authors demonstrate that topical application of moxifloxacin emulgel significantly reduces the severity of psoriatic lesions, as assessed by PASI scores and histological examination. Furthermore, they report that moxifloxacin treatment leads to a decrease in pro-inflammatory cytokines (TGF-β, TNF-α, IL-17, IL-1β, IL-23, and VEGF) and an increase in anti-inflammatory cytokines (IL-10 and IL-37). The drug also appears to alleviate oxidative stress, suppressing oxidative indicators, and elevating antioxidant enzyme levels. These findings align with previous research highlighting the immune-modulatory, anti-oxidative, anti-inflammatory, and anti-mitotic properties of fluoroquinolones [15,18].

The observed effects of moxifloxacin are likely multifactorial. Fluoroquinolones have been shown to inhibit phosphodiesterases (PDEs), leading to increased intracellular cAMP concentrations and subsequent suppression of pro-inflammatory cytokine production [14]. They can also interfere with the activation of key transcription factors like NF-κB, a central regulator of inflammatory responses. Moreover, moxifloxacin has demonstrated anti-proliferative and pro-apoptotic effects in various cell types, potentially contributing to the reduction in psoriatic lesions [15].

While the study's focus is on the dermatological aspects of psoriasis, the implications for neurology warrant consideration. Neuroinflammation is a key feature of many neurological disorders, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and stroke [19]. Cytokines like TNF-α, IL-1β, and IL-17, which are reduced by moxifloxacin in the psoriasis model, play a significant role in driving neuroinflammation and neuronal damage. Therefore, the potential of moxifloxacin to modulate these cytokines could be relevant in the context of neurological diseases.

Furthermore, oxidative stress is a major contributor to neurodegeneration [20]. The ability of moxifloxacin to suppress oxidative stress, as demonstrated in the study by Abbas *et al.*, could be neuroprotective.

Drug repurposing, as the authors note, is a valuable strategy for accelerating the development of new treatments. Given the established safety profile of moxifloxacin as an antibiotic, exploring its potential for treating inflammatory neurological conditions could be a worthwhile endeavor. However, several caveats must be considered.

First, the imiquimod-induced psoriasis model in mice has limitations in fully replicating human psoriasis. The model exhibits acute symptoms without the chronic relapsing nature of human disease. Therefore, the findings need to be validated in other experimental models and, ultimately, in human clinical trials. Second, the study by Abbas *et al.* focuses on the topical application of moxifloxacin. While this route of administration may be suitable for psoriasis, it may not be optimal for neurological conditions, where systemic delivery and blood-brain barrier penetration are important considerations.

Third, the potential neurotoxic effects of fluoroquinolones need to be carefully evaluated. While Moxifloxacin is generally considered safe, fluoroquinolones have been associated with neurological side effects in some individuals [21]. This is a significant caveat that needs careful evaluation. These side effects can range from mild, such as dizziness and headaches, to more severe, including seizures, neuropathy, and psychiatric disturbances [22]. The mechanisms behind these neurotoxic effects are not fully understood but may involve interactions with the GABA receptors in the brain. As selective antagonists of GABAA receptors, fluoroquinolones prevent GABAA receptors from functioning once they are bound. Interestingly, the reduced binding affinity of GABA to its receptor is determined by the side chain substituent in the fluoroquinolone nucleus at position R7. GABA is one of the main inhibitory neurotransmitters in the central nervous system. When fluoroquinolones are present, GABA might not effectively inhibit its target, which could cause the central nervous system to become overactive [23]. A study conducted in rats suggested that rodents treated with ciprofloxacin had a significant decrease in GABA levels in brain tissue when compared to a control group, and showed depression and anxiety-like behaviors [23,24]. Furthermore, the blood-brain barrier penetration of moxifloxacin, while necessary for treating neurological infections, could also contribute to these adverse effects by allowing the drug to directly

interact with neuronal tissue [24]. Therefore, a thorough risk-benefit assessment, including preclinical and clinical studies specifically designed to evaluate neurological safety, is crucial before considering moxifloxacin for treating neurological conditions. Despite these limitations, the study by Abbas *et al.* provides a compelling rationale for further investigating the potential of moxifloxacin and other fluoroquinolones in the context of neuro-immunological disorders. Future research should focus on:

- Evaluating the effects of moxifloxacin on neuroinflammation and neurodegeneration in relevant animal models of neurological diseases.
- Investigating the mechanisms by which moxifloxacin modulates neuro-immune interactions.
- Determining the optimal route of administration and dosage of moxifloxacin for neurological applications.
- Assessing the safety and efficacy of moxifloxacin in human clinical trials for specific neurological conditions.

In conclusion, while the study by Abbas *et al.* primarily addresses the dermatological aspects of psoriasis, it raises intriguing questions about the potential for moxifloxacin to modulate inflammatory pathways relevant to neurological disorders. Further research is needed to fully explore this potential, but the study provides a valuable starting point for investigating the neuro-immunological effects of this widely used antibiotic. This highlights the importance of interdisciplinary research and the potential for unexpected therapeutic applications of existing drugs.

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