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Azithromycin Shows Anti-Zika Virus Activity in Human Glial Cells

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We read with interest the manuscript by Saiz and Martín-Acebes (1) on the candidate drugs with *in vitro* anti-Zika virus activity. The drugs presented in that review belong to several classes, such as antibiotic, antiviral, antimalarial, and antiparasitic agents, immunosuppressant and immunomodulating drugs, proteasome inhibitors, antidepressants, antiemetic agents, cyclin-dependent kinase inhibitors, apoptosis-related drugs, and hypolipidemic agents (1). Among the antibiotics with an *in vitro* anti-Zika activity, the authors cited nanchangmycin, daptomicin, and kitasamycin, without mentioning azithromycin (an antibiotic of the macrolide family). Indeed, *in vitro* data recently published by Retallack et al. showed that azithromycin was able to reduce the infection rate of U87 cells (a human glioblastoma astrocytoma cell line), to rescue cell viability, and to decrease viral production (2). Although the mechanism of action of azithromycin in inhibiting Zika virus infection of target cells and viral production is still unknown, similar results were obtained using human pluripotent stem cell (hPSC)-derived neural cells infected with Zika virus (2). *In vitro*, azithromycin inhibition activity against Zika virus infection of U87 cells was compared to those of daptomycin and sofosbuvir, two promising candidates that show anti-Zika activities and are considered safe in pregnancy. It was found that azithromycin and sofosbuvir decreased the proportion of infected cells to below 5%, while daptomycin was unable to decrease the infection rate below 46% in this experimental model, even at the highest dose (2). Considering the demonstrated antiviral activity in human glial cells, azithromycin represents a candidate molecule for preventing Zika virus-induced alterations of fetal brain. In addition, azithromycin is considered safe during pregnancy and is classified among the FDA category B drugs (3). Pharmacokinetic studies have demonstrated a rapid uptake of this antibiotic in placental tissue (4) and accumulation in human brain (5). Azithromycin represents an interesting and promising molecule for the treatment of Zika virus infections. Besides the antiviral activity demonstrated on human primary cell and cell line cultures, this drug is also a widely diffused and inexpensive antibiotic, available in oral and intravenous formulations. Furthermore, its use is already approved in humans and pregnant women. All these elements strongly support a repurposing approach for azithromycin as an anti-Zika drug for the treatment of infected men as well as infected women, especially during pregnancy. Further studies involving Zika virus-infected individuals are needed and recommended in order to confirm *in vivo* the results previously obtained with *in vitro* experimental models.

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