

Contributor
Annalisa Rubino

Phone
+44 (0) 207 6043078

ABSTRACT/STUDY OVERVIEW

Pregnancy outcomes following systemic prenatal acyclovir exposure: Conclusions from the international acyclovir pregnancy registry, 1984-1999

Acyclovir is commonly used for genital herpes and other herpes virus infections. Since at time of marketing authorization data about potential fetal risk were extremely limited, the Acyclovir in Pregnancy Registry was established in 1984 to monitor pregnancy outcome, including major malformations, in pregnant women exposed to the drug. The registry was a voluntary, observational, prospective, registration and follow up study run in 24 countries from 1984 to 1998.

The registry was publicized to health care providers most likely to diagnose pregnancy. Pregnant women were enrolled and followed up to the end of pregnancy. Pregnancy outcomes were categorized as outcomes with birth defects or without birth defects; subcategories included: live births, spontaneous pregnancy losses (including stillbirths), or induced abortions. Birth defects were coded according to a modification of the CDC definition for birth defects surveillance systems. Prevalence of birth defects observed in the registry was compared with the prevalence of birth defects expected in the general population (i.e. 3.2%).

The registry enrolled a total of 1695 pregnancies exposed to acyclovir; 461 (27%) were lost to follow-up. A total of 1234 pregnancies were followed, with a total of 1246 outcomes. Acyclovir exposure was throughout pregnancy, namely 756 outcomes were exposed in the first trimester, 197 in the second, and 291 in the third trimester. Among live births with first trimester acyclovir exposure, risk of birth defects was 19 of 596 (3.2%; 95% CI, 2.0-5.0%). No unusual defects or pattern of defects were noted. The final analysis report therefore concluded that prevalence (and type) of birth defects observed in outcomes of pregnancies exposed to acyclovir did not differ significantly from those in the general population.

Not only the Acyclovir in Pregnancy Registry generated evidence of relevance for regulatory purposes (see below), but the registry was a landmark study that led the way to several surveillance programs in the following years. Noteworthy the ongoing Antiretroviral in Pregnancy Registry (APR) that is now in its 16th year of monitoring. The APR started in 1989 as the Zidovudine in Pregnancy Registry and was sponsored by the product manufacturer to monitor major teratogenic effects derived from in utero exposure to this antiviral drug. In the subsequent years the APR has included other therapeutics with marketing authorization for the prevention or treatment of infections with the Human Immunodeficiency Virus (HIV) and with the anti-hepatitis B virus (HBV). At its inception the APR registry was an unprecedented multi-sponsored international collaboration between manufacturers and has

case study

Acyclovir: Modified Label

represented a model for subsequent surveillance studies. Currently the APR monitors exposure in pregnancy to 28 marketed antiretrovirals and includes products with an assigned FDA Pregnancy Category B (no evidence of risk in human) or Category C (risk cannot be ruled out) status. Efavinez has Category D status (positive evidence of risk).

A listing of ongoing pregnancy surveillance programs is available from the FDA website (<http://www.fda.gov/womens/registries/registries.html>).

SUPPORT FOR DECISION-MAKING

What type of decision did the study support? How was the study used?

Pregnant women are systematically excluded from clinical trials designed to prove efficacy and safety of experimental drugs. At the time of new drug application with the regulators the vast majority of data available to establish any potential teratogenic effect of a drug is derived from animal studies. Therefore evidence generated in observational studies such as the Acyclovir in pregnancy registry is paramount to assess the safety of drugs in pregnancy and to guide regulatory actions.

At time of marketing authorization Acyclovir was assigned a FDA Pregnancy Category C status (risk cannot be ruled out). However, evidence generated with the Acyclovir in pregnancy registry led the FDA to amend the Pregnancy category status of Acyclovir to the pregnancy category B ((no evidence of risk in human).

Publication Reference(s).

- Stone et al., Birth Defects Res A Clin Mol Teratol. 2004 Apr;70(4):201-7

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