A Review of the Efficacy, Safety, and Pharmacokinetics of Raltegravir in Pregnancy

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Abstract

- Recent pregnancy guidelines recommend raltegravir as a preferred integrase treatment option.
- Data from published articles and preliminary meeting reports between 2001 and July 2015 are reviewed.
- The standard raltegravir dose appears safe and effective in preventing mother-to-child transmission (MTCT) in late pregnancy presenters with unknown or unsuppressed viral load, or in multi-drug resistance.
- Raltegravir was well tolerated. No infant adverse effect was consistently reported.

Methods

- A search was performed on March and June 2015 in EMBASE, Google Scholar, MEDLINE, PubMed, and Web of Science.
- Key words: (raltegravir OR RAL OR Isentress OR MK-0518), (pregnan*) AND (HIV OR HIV-1 OR human immunodeficiency virus)
- Results of all languages, published after 2001, were included.

Results and Discussion

- A total of 278 maternal-infant pairs (69% from retrospective case reports/series, 31% from 3 prospective clinical studies, ~50% peer-reviewed data) were reviewed.
- 87% were from resource-rich settings. Maternal ARV history: 9.3% naive, 33% experienced, 58% not reported. 83% (122/147 cases) received ZDV infusion at delivery and 79% (143/182 cases) underwent Caesarean section.
- Maternal outcomes were not frequently reported. The only consistently reported event was a reversible and transient increase in liver transaminase.
- Most infants were born without adverse outcomes; of the reported events, there was no consistency among type or severity.
- There were two cases where the infant tested positive after birth: one was likely an in utero transmission before initiation of raltegravir, while details on maternal viral load at delivery, drug resistance and adherence were lacking in the second case.

Pharmacokinetic Properties of Raltegravir

- Physiologic changes in pregnancy lowers maternal raltegravir exposures, often with subtherapeutic trough plasma concentrations, but MTCT was not observed.
- Rapid and high transplacental passage, prolonged neonate elimination, and high cervicovaginal fluid: blood plasma ratios contribute to the potential use of raltegravir for infant pre-exposure prophylaxis.
- Adherence may be a factor in the rate of viral decay.

Limitations and Areas for Further Study

- The quality and type of reports available (Table 1) varied significantly, and maternal and infant characteristics failed to be reported in a consistent manner.
- The number of cases reviewed is too small to rule out uncommon toxicities or potential increases in birth defect prevalence in pregnancy, or to generalize findings to the use of alternative integrase inhibitor.

Conclusions

- Due to the inherent pharmacokinetic variability of raltegravir, the highly variable but overall reduced maternal plasma raltegravir levels do not appear to affect viral suppression.
- The viral decay associated with raltegravir treatment is reliably rapid and most women delivered at undetectable viral levels.
- Raltegravir is highly transferred across placenta and has prolonged elimination in the neonate. These two properties support its efficacy in preventing MTCT.
- There is evidence for maternal safety with the exception of transient increase in liver transaminases. However, the relation to raltegravir is unclear.
- No infant adverse effect was consistently reported.
- Raltegravir 400 mg twice daily appears efficacious and safe for both ARV-naive and ARV-experienced pregnant women.

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Declaration of Interest

- AM declares no conflict of interest.
- SW has served on advisory boards and spoken at CME events for AbbVie, Bristol-Myers Squibb, Gilead, Merck and ViiV.
- AT has served on advisory boards and spoken at CME events for Gilead, Janssen and Merck.