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MINIREVIEWS

Antiviral therapy for hepatitis C: Has anything changed for pregnant/lactating women?

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Abstract

Hepatitis C virus (HCV) affects about 3% of the world's population, with the highest prevalence in individuals under 40. The prevalence in pregnant women varies with geographical distribution (highest in developing countries). Prevalence also increases in sub-populations of women at high risk for blood-transmitted infections. HCV infection in pregnancy represents a non-negligible problem. However, most of the past antiviral regimens cannot be routinely offered to pregnant or breastfeeding women because of their side effects. We briefly reviewed the issue of treatment of HCV infection in pregnant/breastfeeding women focusing on the effects of the new direct-acting antivirals on fertility, pregnancy and lactation in animal studies and on the potential risk for humans based on the pharmacokinetic properties of each drug. Currently, all new therapy regimens are contraindicated in this setting because of lack of sufficient safety information and adequate measures of contraception are still routinely recommended for female patients of childbearing potential.

Key words: Hepatitis C virus infection; Breastfeeding woman; Antiviral therapy; Pregnancy category; Direct-acting antivirals

Core tip: Until recently, the only drugs available for the treatment of hepatitis C virus infection had a well-documented teratogenic effect limiting their use in childbearing women. Recently, new generation drugs, designated the direct-acting antivirals have been approved. There are no studies available describing their effects on pregnant and lactating women. We here will try to analyze their pharmacokinetic properties and data from animal studies to try to predict their potential use pregnancy.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a major public health problem that affects more than 150 million people (about 3% of the world's population), most of whom are unaware of their infection[1,2]. The prevalence of HCV infection is between 0.5%-2% in most European countries and in the United States, in which 5-10 million and almost 4 million people, respectively, are affected, most of whom are in the fourth decade of life[1,3-5]. Differently, the prevalence of HCV infection exceeds 10% in some developing countries (especially in Africa, Asia and South America)[1]. One of the modes of HCV transmission is vertical transmission. Rates of vertical transmission of HCV infection range between 2%-10%[4]. Although HCV infection acquired at birth may resolve spontaneously, about 25000 to 50000 of children become chronically infected[4-7]. The prevalence of HCV infection in children is very low in Europe and the United States (0.05%-0.36%)[8], and increases to between 1.8% and 5.8% in Egypt (which has the highest prevalence of pediatric HCV infection), Sub-Saharan Africa, Mongolia and the Amazon Basin[8]. Consequently, birth to an infected mother is one of most frequent routes of infection, and is comparable to injection drug use, unsafe medical practices and high-risk sexual practices[1].

Acute HCV infection, asymptomatic in most cases, can progress to chronic hepatitis in more than half the patients. Chronic hepatitis C is associated with progression to fibrosis, which leads to liver cirrhosis in about 10% to 20% of patients within 20-30 years. Lastly, from about 1%-5% of cirrhotic patients can develop hepatocellular carcinoma each year[2]. Currently, HCV-related liver cirrhosis is the major cause of liver transplantation in developed countries[1,2]. Notwithstanding the decline in the number of cases of acute HCV infection, the burden of liver cirrhosis, hepatocellular carcinoma and HCV-related death remains high due to the existence of a reservoir of infected patients[1,3].

The epidemiology of hepatitis C infection might change radically in the next few years thanks to antiviral therapies that result in viral clearance in terms of sustained virologic response (SVR), namely undetectable HCV RNA 12 wk (SVR12) or SVR24 after treatment completion. HCV infection is cured in more than 99% of patients who achieve an SVR. Generally, liver disease can be cured only in non-cirrhotic patients[2].

The effect of maternal viremia on vertical transmission and on the rate of spontaneous resolution of the acquired infection among newborns is not well defined. However, mothers with undetectable plasma HCV RNA levels rarely transmit HCV by the vertical route[4]. Therefore, it seems reasonable to assume that treatment to decrease viremia in pregnant women with chronic HCV may result in lower rates of vertical HCV transmission.

Until 2011, the standard-of-care therapy for HCV infection, which was based on the association of pegylated interferon (PEG-IFN) and Ribavirin, resulted in an SVR in only 40%-80% of patients depending on HCV genotype (lower for genotypes 1 and 4 than for genotypes 2 and 3)[2]. In 2011, new antiviral drugs, namely, direct-acting antivirals (DAAs), became available. These drugs act mainly by targeting the non-structural HCV proteases NS3-4A and NSA5 or by inhibiting RNA-dependent RNA polymerase, and are thus referred to as protease inhibitors and inhibitors of HCV RNA-dependent RNA polymerase, respectively[2]. Each of these DAAs can be used as a component of combination regimens (with or without PEG-IFN and Ribavirin) and result in SVR rates as high as 60%-100%[2]. The SVR rate depends on the DAA used, the HCV genotype, pre-existing amino acid substitutions (that might confer resistance to some DAAs) and the severity of liver disease[2]. These new regimens could change both the epidemiology and the natural progression of hepatitis C.

Here we discuss the potential use, in pregnant and breastfeeding women, of the antiviral therapies (including DAAs) licensed for the treatment of chronic C hepatitis. We also examine the adverse effects of anti-HCV drugs on fertility, pregnancy and lactation (in particular, embryo toxic and teratogenic effects). In this context, no antiviral therapy has yet been approved for use in childbearing women, and therefore little is known about the effects of anti-HCV drugs on pregnancy and lactation in this population. Consequently, our discussion and conclusions are based principally on data derived from animal studies[9-15].

ANTIVIRAL THERAPY OF HEPATITIS C IN CHILDBEARING WOMEN

Hepatitis C infection in pregnant and breastfeeding women is not a negligible problem. About 1%-8% of pregnant women have markers of HCV infection, and the prevalence is lower in western/northern countries than in Eastern/Southern countries[11,15]. Since, HCV infection is usually asymptomatic, most infected women are unaware of their status and may be diagnosed with chronic C hepatitis incidentally when undergoing serological tests during pregnancy or before delivery. For example, in Italy, free-of-charge screening for HCV, HBV and the human immunodeficiency virus, is routinely offered to all pregnant women from the 33rd to the 37th week of gestation[16] and reveals many cases of previously undiagnosed chronic C hepatitis. Notably, the number of HCV-infected childbearing women is expected to increase with the increase in the migratory flow from developing countries to Western/Northern countries. As mentioned above, the vertical transmission

of HCV infection is now one of most frequent routes of transmission[1]. Consequently, eradication of the virus in pregnant women and women of childbearing age is the main target in the prevention and control of HCV infection[4]. Problems related to the treatment of HCV infection in pregnant and breastfeeding women are not rare. In a developed country such as the United States, pregnancy is the third most common contraindication to treatment and delayed treatment onset in about 2% of more than 45000 HCV-infected patients[17]. In addition, in the same study about 1.3% of women undergoing antiviral therapy for HCV became pregnant during therapy[17]. Thus, the problem is not only whether or not to start treatment in a pregnant and/or breastfeeding woman, but also how to manage a woman who becomes pregnant during antiviral therapy.

The past of antiviral therapy: PEG-IFN/Ribavirin and PEG-IFN/Ribavirin plus first-generation DAAs

For many years, the two cornerstones of the standard-of-care treatment of HCV infection were IFN and Ribavirin, both of which have side-effects and contraindications that limited their use in the setting of pregnant/breastfeeding patients[18,19]. IFN-α is a protein released in response to viral infections. It binds to specific receptors on the cell surface thereby promoting a complex cascade of protein-protein interactions that rapidly activate gene transcription. IFN-stimulated genes regulate many biologic effects (*i.e.,* inhibition of viral replication in infected cells, inhibition of cell proliferation and immunomodulation). The United States Food and Drug Administration (FDA) classified the first pharmacological formulation of IFN-α in Pregnancy Category C since the molecule had an abortifacient effect in animals (rhesus monkeys) during the early/middle fetal period of organogenesis and late fetal development[20,21]. The drug may also impair fertility; in fact, menstrual cycle irregularities, namely, prolonged or shortened menstrual periods and erratic bleeding, have been observed in nonhuman primates, and menstrual rhythm normalized upon treatment discontinuation[22]. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte IFN although no mutagenic effect or toxicity has been reported[22]. Given the species-specificity of IFN, effects in animals are unlikely to be predictive of those in humans[20,21]. Nevertheless, in clinical practice, IFN-α is widely used in most pregnant women affected by essential thrombocythemia to prevent or reduce the risk of thrombocythemia-related fetal loss[22]. The risk of major malformation, miscarriage, stillbirth or preterm delivery does not seem to be significantly higher in this setting than in the general population[22].

Also the pegylated formulation of IFN-α (PEG-IFN-α) should be assumed to have abortifacient potential despite the lack of well-controlled studies in pregnant women[23,24]. Apart from the potential risks for the fetus, a major concern is the risk of serious IFN-related adverse effects on the patient's psychological status, namely exacerbation of postpartum depression[18]. Therefore, pregnant candidates for PEG-IFN treatment should undergo psychiatric evaluation. The degree of IFN excretion in human milk is unknown. However, given the potential risk of serious adverse reactions to the drug in nursing infants, IFN is contraindicated in children below the age of 2 years[20,21,23,24]. The decision whether to discontinue nursing and to initiate antiviral therapy depends solely on whether or not the progression of maternal liver disease must be immediately blocked. Given its low SVR rate (< 30%), PEG-IFN mono-therapy has been widely used in recent years in association with Ribavirin[25]. The combination of PEG-IFN and Ribavirin increased the SVR24 to 40% in North America and to 50% in western Europe in patients infected with HCV genotype 1[25]. Even better results were obtained in patients with genotypes 2, 3, 5 and 6: The best SVR was achieved in patients with genotype 2 (up to 80% SVR)[25]. The results of combined treatment in genotype 4 patients are the same as those obtained in genotype 1 patients or slightly better[25].

Ribavirin is a guanosine analog nucleotide inhibitor that acts by interrupting viral RNA synthesis and viral mRNA capping. It is a prodrug that, when metabolized (into purine RNA nucleotides), interferes with RNA metabolism required for viral replication[26,27]. The mechanism underlying this effect is unknown. The FDA classified Ribavirin in Pregnancy Category X[26,27] because of its embryocidal and teratogenic effects in animals[26-28]. The fetal malformations reported in animal studies include abnormalities of the skull, palate, eye, jaw, limbs, skeleton and gastrointestinal tract[26-28]. Therefore, Ribavirin is absolutely contraindicated for both HCV-infected childbearing women and HCV-infected male partners of pregnant women unless they take effective contraceptive measures. In addition, since Ribavirin-induced spermatogenic abnormalities (cell toxicity, mutagenicity and a decreased epididymal sperm count) reverted only 4-8 mo after treatment withdrawal in all animal species studied[29,30], women are advised to avoid pregnancy for at least 6 mo after partners of men taking Ribavirin treatment[26,27].

Between 2003 and 2009, the United States Ribavirin Registry collected the data of 118 babies born to mothers exposed to the drug (49 direct and 69 indirect exposures) during pregnancy: Only six cases of birth defects were reported (torticollis, hypospadias, polydactyly, neonatal teeth, glucose-6-phosphate dehydrogenase deficiency, ventricular septal defect, and cyst of the fourth ventricle of the brain)[28]. Despite the low rate of birth defects, it seems reasonable not to encourage or support the use of Ribavirin in pregnant women, and, moreover, to recommend that women avoid pregnancy during Ribavirin treatment.

In conclusion, because of its low SVR rate unless combined with Ribavirin, PEG-IFN should not be administered in childbearing women even though it has not been reported to have abortifacient and/or teratogenic effects.

Table 1 Main pharmacokinetic properties of the new direct-acting antivirals

Drug		Molecular weight	Effect of food on absorption	Cytochrome P450 enzymes interaction			Binding to plasma protein	Half-life
				Enzyme	Effect of the drug on the enzyme	Effect of the enzyme on the drug		
Sofosbuvir		529.45 Da	Increased absorption, slower rate	NO	None	None	85%	0.5 h/26 h[1]
Simeprevir		749.93 Da	Increased absorption, slower rate	CYP3A4	Inhibitor	Alter AUC	> 99.9%	10-41 h
Daclatasvir		738.98 Da	Decreased absorption[2]	CYP3A4	Weak inducer	Alter AUC	> 99%	12-15 h
Ledipasvir		888.9 Da	No effect	CYP3A4	Weak inducer	None	> 99.8%	47 h
Viekirax	Ombitasvir	894.1	Increased absorption	CYP3A4	Inhibitor	Alter AUC	99.9%	21-25 h
	Paritaprevir	765.8 Da					98.6%	5.5 h
	Ritonavir	720.9 Da					99%	4 h
Dasabuvir		493.5 Da	Increased absorption	CYPC19	Inducer	None	99.5% (94.5%[3])	6 h
				CYP2C8	None	Alter AUC		
				CYP3A4	None	Alter AUC[3]		
				CYPC19	Inducer	None		

[1]GS-331007 metabolite; [2]Following a high-fat meal; [3]Dasabuvir M1 metabolite. AUC: Area under the curve; NO: Not metabolized by P450 enzymes; CYP: Cytochrome.

The year 2011 saw the advent of DAAs that target essential components of the HCV life cycle. The first-generation DAAs were the protease inhibitors boceprevir and telaprevir, which were indicated mainly for the treatment of chronic hepatitis C patients infected by genotype 1 virus. Boceprevir is an inhibitor of HCV NS3/4A protease, an enzyme required for the proteolytic cleavage of HCV-encoded polyprotein into mature forms of the non-structural proteins NS4A, NS4B, NS5A and NS5B. Telaprevir is an NS3-4A protease inhibitor that competes with NS5A/5B for its substrate-binding site. The FDA classified both these first-generation DAAs in Pregnancy Category B[31,32]. In fact, neither boceprevir nor telaprevir negatively affected fetal development in animals (mice, rats and rabbits). Consequently, in the absence of well-controlled human studies, "no evidence of risk in humans" has been supposed. Nevertheless, the major limitation to the use of these drugs is that they must be administered in association with PEG-IFN and Ribavirin as part of a triple-therapy regimen. Consequently, both boceprevir and telaprevir are contraindicated during pregnancy and adequate contraceptive measures are strongly recommended for both childbearing women and their male sexual partners throughout treatment duration and up to 6 mo after withdrawal[31,32]. Lastly, the excretion of protease inhibitors into human breast milk remains to be clarified; the levels of these drugs in the milk of lactating rats can be higher than those observed in maternal blood[31,32].

Second-generation DAAs

The second-generation DAAs, which became available in 2015, and their principal pharmacokinetic properties are listed in Table 1. Pharmacokinetic data are not complete for all second-generation DAAs. In the absence of data on their properties and effects on pregnant and lactating human females, clinicians can only try to predict the effect that pregnancy-associated physiological changes may have on the peak plasma dose, drug metabolism, and the ability of the drug to cross the placental barrier and/or enter into the mother's milk. Generally, drugs that are more likely to cross the placenta are lipids or weak acids with a molecular weight below 500 Da, are poorly bound to plasma proteins and have a long half-life. The concentration of the drug in breast milk, and therefore its potential effect on the newborn, depends on dosage, rate of absorption in the maternal circulation, maternal drug metabolism and the time from drug administration to breastfeeding[33,34]. In the following section we will briefly review the data on the pharmacokinetics and teratogenicity in animals of the DAAs currently available to try to identify the ones that could potentially be used in childbearing women.

Sofosbuvir (Sovaldi®) is a pangenotypic nucleotide prodrug converted by hepatocytes into its active form that acts by competitively inhibiting the HCV NS5B polymerase active site and thus blocking viral RNA synthesis. It is indicated for the treatment of chronic hepatitis C as a component of a combination antiviral regimen. Neither the area under the curve (AUC) nor the product's absorption changes when the drug is taken with food, which suggests that the prolonged gastric emptying observed in pregnancy would not affect absorption of the drug or the time-to-peak plasma dose. Sofosbuvir is readily available after oral administration, and undergoes extensive first pass metabolism. Gender does not appear to significantly affect its pharmacokinetics[35]. Since P450 enzymes do not seem to be involved in metabolizing Sofosbuvir, increased activity of these enzymes in pregnancy is unlikely to affect its plasma concentration. On the other hand, Sofosbuvir has strong affinity for the P-glycoprotein efflux protein (Table 1). The drug is eliminated as GS-331007 in urine. The glomerular filtration rate usually increases during pregnancy and consequently renal drug elimination is generally greater than elimination in the non-pregnant state; however, it is unclear whether this process could alter the plasma concentration of Sofosbuvir to the point of requiring dose adjustment to attain a clinical response. Similarly, it is unclear whether the drug could cross the placental barrier. In studies conducted on animals (rats and rabbits), Sofosbuvir

Table 2 Effect of new direct-acting antivirals in pregnancy and Food and Drug Administration Pregnancy Categories

Drug		Embryotoxicity and/or teratogenicity[1]	Dose-escalation[2]	Transfer across placenta	Transfer into milk	FDA Pregnancy Category[3]
Sofosbuvir		No	28-fold	Yes	Yes	B
Simeprevir		Yes	4-fold	Yes	Yes	C
Daclatasvir		Yes	4-fold	Yes	Yes	NA[4]
Ledipasvir		No	Maternal toxic doses	Yes	Yes	B
Viekirax	Ombitasvir	Yes	4-fold	Minimal	Yes	B
	Paritaprevir		32-fold			
	Ritonavir		8-fold			
Dasabuvir		No	48-fold	Minimal	Yes	B

[1]Based on animal studies; [2]Dose escalation above therapeutic dose; [3]FDA Pregnancy Category without association with ribavirin. NA: Not available; FDA: The Food and Drug Administration.

metabolites crossed the placenta and entered the milk of lactating animals. However, this process did not appear to significantly affect the viability or the development of embryos or fetuses[34,35]. Little is known regarding the use of Sofosbuvir in pregnant women. The outcomes of less than 300 pregnancies are mentioned in the product characteristics reports of the European Medical Agency, but no data about those outcomes are available on the Pubmed database. The FDA classified Sofosbuvir in Pregnancy Category B when used alone or with Ledipasvir, and in Pregnancy Category X when used in combination with Ribavirin. The latter combination is strongly contraindicated during pregnancy and adequate contraceptive measures are highly recommended for both childbearing women and their male sexual partners throughout treatment duration and up to 6 mo after treatment withdrawal (Table 2)[36].

Simeprevir (Olysio®) is a specific NS3/4A HCV serine protease inhibitor that interrupts the processing of the HCV-encoded polyprotein thereby blocking the HCV viral life cycle. Simeprevir is considered a second-generation HCV protease inhibitor because its binding affinity and specificity for NS3/4A is higher than that of first-generation protease inhibitors that have a linear structure. It has been approved as part of combination regimens with PEG-IFN and Ribavirin or with Sofosbuvir for the treatment of chronic hepatitis C genotype 1 infection in adults. When Simeprevir is taken with food, its absorption is delayed so that its bioavailability reaches 62% (Table 1). It is therefore possible that the prolongation of gastric emptying observed in pregnancy may also affect absorption and the time-to-peak plasma dose of Simeprevir. After its absorption, Simperevir undergoes first-pass metabolism by the P450 cytochrome enzymes, mainly the CYP3A4 system (Table 1). It is also a substrate of the P-glycoprotein drug transporters. Plasma levels of Simeprevir change significantly when administered with inducers or inhibitors of CYP3A4. Plasma exposure of simperevir is greatly affected also by the state of the liver, and there may be an increase of up to 5-fold in the AUC depending on the degree of hepatic impairment. Therefore, the increased activity of the P450 enzymes in pregnancy, and the possible physiopathological changes that may affect the liver of pregnant women may affect the plasma concentration of Simeprevir. Metabolites of Simeprevir are mainly eliminated *via* biliary excretion. Gender did not appear to have a clinically relevant role on the pharmacokinetics of Simeprevir.

As yet, there are no data concerning the passage of Simeprevir across the human placenta (Table 2), however, animal studies established that the drug is transferred across the placenta, and that it exerts teratogenic effects on the foetal skeletal system, namely supernumerary ribs and delayed ossification at exposures 4-fold higher than those observed at the recommended dose (Table 2). Moreover, Simeprevir can be excreted in the milk of lactating animals. The drug is classified in FDA Pregnancy Category C when administered alone, and Pregnancy Category X when used in combination with Ribavirin[37-39].

Daclatasvir (Daklinza®) inhibits the NS5A protein (Table 1), and appears to act on viral replication, and on the assembly and secretion stages of the viral life cycle, thereby causing a rapid decline in both intra- and extracellular levels of HCV RNA. It is the first NS5A complex inhibitor approved for use in the European Union as part of combined regimens with Sofosbuvir, Ribavirin and PEG-IFN for the treatment of chronic HCV infection in adults. Oral clearance (CL/F) of Daclatasvir is significantly lower in women than in men[40]. However, this gender difference does not appear to be clinically relevant. It remains unclear whether the documented non-significant gender difference in oral clearance, and the expected changes in drug bioavailability and clearance in the pregnant state may, together, significantly affect Daclatasvir exposure in pregnant women.

Daclatasvir is a substrate of P-glycoprotein and is metabolized by the CYP3A4 enzyme (Table 1). Dose adjustments are recommended when it is administered with strong inducers of this class of cytochrome enzymes. It is therefore likely that the increased activity of the P450 enzymes in pregnancy would affect the plasma concentration of Daclatasvir.

Daclatasvir is primarily excreted unchanged through the biliary route. Overall, based on its chemical characteristics, it is unlikely that Daclatasvir could cross the materno-fetal circulation at therapeutic doses. However,

Daclatasvir was found to cross the placenta in a study conducted in rats and rabbits[40] (Table 2). In the latter study, there was a decrease in the gestational weight of mothers exposed to the drug. Daclatasvir exerted an embryotoxic and teratogenic effect at exposures 4-fold to 16-fold higher than the clinical AUC exposure, and the potential toxic exposure was exponentially greater with the increase in the animals' body surface area[40]. In other studies, Daclatasvir was excreted in the milk of lactating animals at concentrations 1.7- to 2-fold higher than maternal plasma concentrations[40,41-43]. Daclatasvir has recently received FDA approval for marketing in the United States. At the time of writing this article, it has not been included in a Pregnancy Category.

Ledipasvir is available in a combined formulation with Sofosbuvir called Harvoni. Harvoni is administered alone or in combination with Ribavirin in patients with chronic hepatitis C infection[2]. Ledipasvir acts on the replication, assembly and secretion phases of HCV by inhibiting HCV NS5A phosphoprotein[44]. Based on the limited data available, Ledipasvir acts only on genotypes 1, 3 and 4. It is gradually absorbed after oral administration; the AUC does not appear to be affected when the drug is administered with meals. Moreover, Ledipasvir does not appear to undergo significant first pass and/or pre-excretory metabolism and it is mainly excreted unchanged through the biliary route, in faeces. Like Sofosbuvir, Ledipasvir is not metabolized by the P450 enzymes. It is therefore unlikely that increased activity of these enzymes in pregnancy affects its plasma concentration. Slow oxidative metabolism of Ledipasvir into M19 has been demonstrated *in vivo*, although the mechanism underlying this process is unknown. However, it is not possible to make any assumption regarding changes in this particular metabolic route in pregnant women. Both the AUC and C-max of Ledipasvir appear to be greater in females than in males, but this difference has not been considered clinically significant by the regulating authorities[44] (Table 1).

Studies conducted with animals showed that Ledipasvir crosses the placenta and is excreted in the milk of lactating animals. In non pregnant animals, the number of corpora lutea and implantation sites were decreased with a 6-fold increase in exposure, while in pregnant animals the effects on offspring, *i.e.,* mainly alterations in body weight, were observed at a concentration 4-fold higher than the recommended clinical dosage[44]. The FDA categorized Ledipasvir in the Pregnancy Category B when used with Sofosbuvir without Ribavirin[42-44] (Table 2).

Viekirax® is a combination formulation composed of three pharmacologically active substances, namely Ombitasvir, Paritaprevir and Ritonavir. The combination acts on different steps of the HCV lifecycle: Ombitasvir inhibits HCV NS5A and Paritaprevir inhibits HCV NS3/4A, while Ritonavir, which does not directly affect HCV, acts as a booster of Paritaprevir through its inhibitory effect on CYP3A. Viekirax is indicated only in combination with Ribavirin and/or Dasabuvir (see below) for the treatment of chronic hepatitis C in adults. The combination reaches T-max 4-5 h after oral administration and requires up to 12 d of dosing to reach steady state[45,46]. Exposures of the individual components are affected by drug-to-drug interactions, even with the other components of Viekirax and with Dasabuvir. Food also significantly affects Viekirax absorption. In fact, absorption of the drug is much lower when administered in the fasting state. All three components are highly-bound to plasma proteins and undergo extensive hepatic metabolism. Notably, Paritaprevir is predominantly metabolized by CYP3A4, and therefore requires boosting with Ritonavir, which is also metabolized by the same enzyme. The components of the combination have different half-lives: Ombitasvir has the longest half-life, around 21-25 h and is mainly excreted by the biliary route. Paritaprevir and Ritonavir have a mean half-life of 5.5 and 4 h, respectively and are excreted mainly in faeces with only a small proportion being eliminated renally (8.8% for Paritaprevir and 11.3% for Ritonavir). Since exposures of the three individual components of Viekirax do not seem to vary significantly irrespectively of the degree of renal impairment, therefore renal elimination does not appear to be significant. Exposure of all the three active components of Viekirax is related to gender. In fact, concentrations of Ombitasvir and Paritaprevir were found to be 0.5- and 1-fold higher, respectively in women[47]. Moreover, exposure of Ombitasvir was found to be related to body weights. Body weight also affects Ombitasvir exposure but not Paritaprevir exposure (Table 1).

Both Ombitasvir and Paritaprevir/Ritonavir caused malformations in the eyes and teeth of animals at exposures 4-fold higher than the AUC. In the case of Paritaprevir/Ritonavir, an exposure 32/8-fold higher than those observed at the recommended dose resulted in malformation in the offspring of animals, again involving the eyes. Passage of Ombitasvir and Paritaprevir metabolites in the milk of lactating animals, and to a lesser extent through the placenta, has been demonstrated, but no effect was observed in lactating pups. The FDA categorized Viekirax in Pregnancy Category B[45-47] (Table 2).

Dasabuvir (Exviera®) is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase. It is indicated for the treatment of chronic hepatitis C infection in adults only in combination with Viekirax, thereby forming the "Viekira pak". Dasabuvir reaches T-max 4-5 h after oral administration. Viekira pak reaches steady state after 12 d of dosing. Like Viekirax, Dasabuvir must be administered with food. In fact, taken with food, its exposure is 30% higher than in the fasting state. It is metabolised by the P450 enzymes, namely CYP2C8 and to a lesser extent by CYP3A. Its metabolites are mainly eliminated through the biliary route. Exposure is 30% higher in women than in men. Also Dasabuvir exposure is affected by body weight and by impairment of renal and hepatic functions, albeit not in a clinically significant way (Table 1).

At doses of Dasabuvir 48-fold higher than the maximum recommended dose, Dasabuvir did not cause any embryocidal and/or teratogenic effects in animals[47]. The drug was excreted in the milk of lactating animals probably by the breast cancer resistance protein efflux transporter of which Dasabuvir is a substrate. However, the drug did not affect nursing pups. The FDA categorized Dasabuvir in Pregnancy Category B[45,46,48] (Table 2).

CONCLUSION

Given the lack of human studies, no DAA has yet been approved for use in pregnancy or during breast feeding. Consequently, we have reviewed the features of the DAAs approved for treatment of chronic HCV infection in adults in the attempt to identify the most promising candidates, in terms of pharmacokinetic profile and adverse effects, for use in pregnancy or during breast feeding. Sofosbuvir appears to have a favourable pharmacokinetic profile and animal studies indicate that it may be safe during pregnancy. Thus, Sofosbuvir, used in Ribavirin-free regimens, may become the drug of choice for women of childbearing age affected by HCV infection. On the contrary, Simeprevir is not suitable for use in pregnant or breast-feeding women, because its AUC and half-life are greatly affected by liver performance and by drug-drug interactions. Moreover, Simeprevir was associated with teratogenic effects in animals at doses only 4-fold higher than recommended doses. Ledipasvir has a highly favourable pharmacokinetic profile, and too moreover was safe in animal embryos and fetuses. Consequently, its combined formulation with Sofosbuvir (Harvoni), appears to be a good choice in women of child-bearing potential. Daclatasvir, based on its pharmacokinetic profile, appears to have a wide safety margin when used at therapeutic levels. It also appears that dosages may have to be increased in pregnant women. However, in contrast to its expected safety, it was found to cross the placenta and exert a teratogenic effect in animals. It is still awaiting FDA pregnancy categorization.

Although the Ombitasvir/Paritaprevir/Ritonavir combination is in FDA Pregnancy Category B, the pharmacokinetic profile of the individual components, namely absorption and affinity for P450 enzymes, suggest a potential for variability in AUC exposures with the physiological changes of pregnancy to the point that dose adjustment may be required. Furthermore, the components of the combination exerted a teratogenic effect on animals. Lastly, given its indication for use in combination with Ribavirin, it would not be suitable for women of childbearing potential. Dasabuvir is supposed to be relatively safe in pregnancy based on its pharmacokinetic profile and animal studies.

Until very recently infection with HCV genotype 2 would have posed a further treatment challenge in infected pregnant women, because all the recommended regimens for its treatment included Ribavirin. Even though Italian authorities have very recently approved the use of Daclatasvir for the treatment of adult patients chronically infected by HCV genotype 2 in Ribavirin-free regimen associated with Sofosbuvir[49], a safety data on pregnant women are lacking.

In conclusion, second-generation anti-HCV DAAs have revolutionized the standard of care and prognosis of patients suffering from chronic hepatitis C infection, however, childbearing women cannot benefit from this advance. As concluded by other authors[4], despite promising safety profiles, there are no approved therapies to prevent vertical HCV transmission. Therefore the only achievable goal seems to be universal screening of fertile women to identify and treat those with HCV infection before they become pregnant.

Lastly, it would be useful to create a registry similar to the Ribavirin Pregnancy Registry in order to monitor the effect of the second-generation DAAs on women who become pregnant during therapy, in terms of outcome on both the mother and the product of conception.

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