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BRIEF REPORT

Post-licensing safety of fosamprenavir in HIV-infected children in Europe†

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ABSTRACT

Purpose Fosamprenavir, combined with low-dose ritonavir (FPV/r), is indicated for treatment of HIV-infected children aged ≥6 years in Europe. Our purpose was to assess the safety of licensed use of FPV/r in HIV-infected children reported to six cohorts in the European Pregnancy and Paediatric HIV Cohort Collaboration.

Methods Retrospective analysis of individual patient data for all children aged 6–18 years taking the licensed dose of FPV up to 31/12/10. Adverse events (clinical events and absolute neutrophil counts, total cholesterol and triglycerides, and alanine transaminase) were summarised and DAIDS gradings characterised severity.

Results Ninety-two HIV-infected children aged 6–18 years took the licensed dose, comprising 3% of the total number of children in follow-up in participating cohorts. Median age at antiretroviral therapy initiation was 6 years (interquartile range 1–11 years), and median age at start of FPV/r was 15 years (12–17 years). Estimated median time on an FPV-containing regimen was 52 months, with a total of 266.9 patient years of exposure overall. Half (54%) were on an FPV-containing regimen at last follow-up. Rates of grade 3/4 events were generally low for all biochemical toxicity markers, and no serious adverse events considered to be causally related to FPV/r were reported.

Conclusions Results suggest that long-term licensed dose FPV-containing regimens appear to be generally well tolerated with few reported toxicities in HIV-infected children in Europe, although relatively infrequently prescribed. No serious events were reported.

KEY WORDS—pharmacovigilance; epidemiology; fosamprenavir; safety; HIV; children; pharmacoepidemiology

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INTRODUCTION

Fosamprenavir (FPV, Telzir™), combined with low-dose ritonavir (FPV/r), was approved in Europe for treatment of HIV-infected children aged ≥6 years in 2007. Dosing is by weight: 18/3 mg/kg twice daily (BID) up to a maximum of 700/100 mg for liquid formulations; for children ≥39 kg, 700/100 mg BID for tablets.

Safety data from three FPV clinical trials in children (APV20003, APV29005, and APV20002) have been reported.[1–3] Findings indicate that infections/infestation and gastrointestinal events were the most commonly reported adverse events (AEs). Treatment-emergent grade 3/4 neutropenia was reported in less than 20% of children across the studies but were considered unlikely to be related to FPV.[4] However, only one study

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to date has assessed FPV/r in routine clinical practice. Palladino *et al*. studied 20 HIV-infected children over a median of 180 weeks and reported sustained antiviral response and immunological improvement.[5]

We conducted a pharmacoepidemiology study to assess the use and long-term safety of FPV in children in 'real world' clinical settings in Europe. Individual patient data originated from cohorts participating in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC), a network of European cohorts of prospectively observed mother–child pairs and children within EuroCoord (www.eurocoord.net).[6]

METHODS

Six cohorts participated in this study and reported data for children aged 6–18 years who had ever taken FPV/r to the end of 2010. Ethical approval was granted for the study.

Children were considered to be on the licensed dose if aged 6–18 years when taking FPV within a window of +/−20% of the licensed dose of 18 mg/kg BID, or on the adult dose (700 mg BID, weight >39 kg), taken with ritonavir, and outside of pharmaceutical company trials.

The data specification followed the HIV Cohorts Data Exchange Protocol (HICDEP) (www.hicdep.org). Data collected included demographics, deaths, loss to follow-up, antiretroviral therapy (ART) treatment history, AIDS events, biochemistry and AEs, from the start of FPV/r use onwards. In addition, summary characteristics of all children (not just those on FPV/r) in follow-up in each cohort were provided, to estimate the extent of FPV/r use. Further, Intercontinental Medical Statistics (IMS) data on sales volumes of FPV oral suspension were used as a surrogate measure of paediatric exposure. We assumed that most children aged 6–12 years would take fosamprenavir oral suspension rather than tablets because of their body weight (tablets are not suitable for children <39 kg).

Division of AIDS (DAIDS) gradings for paediatric AEs were used to categorise severity of AEs,[7] and rates of grade ≥3 events by time since FPV initiation (<12, 12–24, and >24 months) were estimated (per 100 person years). Analyses focussed on grade ≥3 AEs, and biochemical markers of interest were absolute neutrophil counts (ANC), total cholesterol (fasting) (TC) and triglycerides (fasting) (TG), and alanine transaminase (ALT). Clinical serious AEs were collected and coded using MedDRA. Other non-serious AEs (e.g., headache and gastrointestinal problems) were not included as they were not consistently collected by the participating cohorts. All analyses were undertaken using Stata version 12.0 (Stata Corp, College Station, TX, USA).

RESULTS

Ninety-two children took the licensed dose of FPV. Additionally 20 children took FPV off label, of whom 15 were aged 6–18 years and took an unlicensed dose, and 5 were aged <6 years; these children are not described further in this report. Of the 92 on the licensed dose, 28 (30%) were from Belgium, 27 (29%) from Italy, 23 (25%) from Romania, 11 (12%) from Spain, and 3 (3%) from the UK/Ireland. The total number of children aged 6–18 years in follow-up in these cohorts during 2007 to 2010 was 2673, giving an overall prevalence of 3% taking the licensed FPV dose.

Forty-eight children (52%) were male, and of the 65 children with known ethnicity, 29 (45%) were white, and 24 (37%) black African. Among all children, most (71%) were infected with HIV through mother-to-child transmission; 25% infected parenterally were all from the Romanian cohort. A third (33%) of the total had an AIDS diagnosis during overall follow-up.

Median age at ART initiation was 6 years (interquartile range (IQR) 1–11 years), and median age at start of an FPV-containing regimen was 15 years (12–17 years). Estimated median time on an FPV-containing regimen was 52 months, with a total of 266.9 patient years of exposure overall. Half (54%) were on an FPV-containing regimen at last follow-up.

Biochemical toxicity data were available for 82 children. Rates of grade 3/4 events were generally low (Figure 1). For 82 children with ANC results, 57 (70%) had normal results, 11 (13%) grade 1 results, and 6 (7%) grade 2 results. Eight children had grade 3/4 neutropenia, with an overall rate of 5 per 100 person years (95% CI 2–9), and a higher rate in those taking FPV for <12 months (8/100 person years, 95% CI 3–17), although this was not statistically significant compared with those exposed for ≥12 months. Six of the eight children were also taking lamivudine, which is associated with neutropenia. Seven had a normal value following the last grade 3/4 result, and all continued FPV following the grade 3/4 event.

For 78 children with TC results, 32 (41%) had normal results and 22 (28%) grade 1 results. Two children had grade 3 hypercholesterolemia, with an overall rate of events of 4 per 100 person years (95% CI 2–8), and similar rates by duration on FPV; one child subsequently stopped FPV because of non-compliance and dyslipidaemia. An addition of 22 children (28%) had a maximum of grade 2 events.

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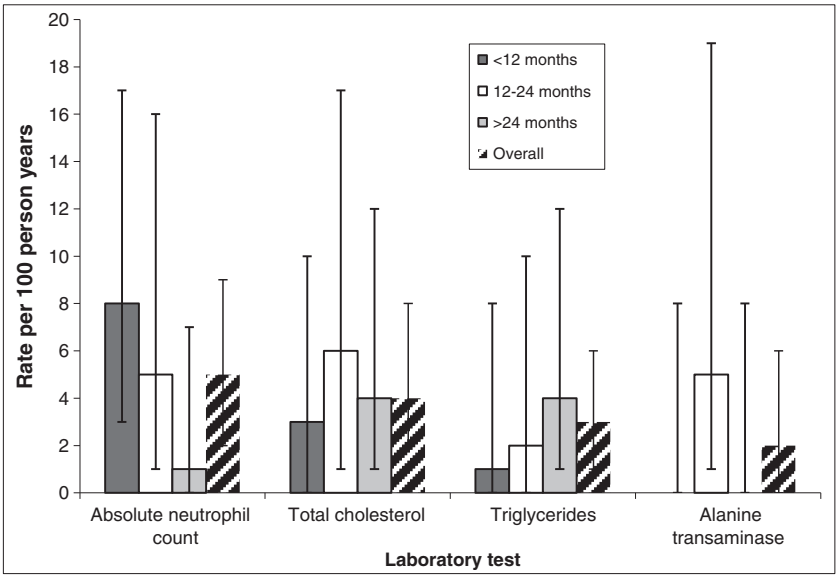

Figure 1. Incidence of grade ≥3 adverse events for key laboratory markers by duration of time on FPV

For 77 children with TG results, 72 (94%) had normal results and three (4%) grade 2 results. Two children had grade 4 hypertriglyceridemia, with an overall event rate of 3 per 100 person years (95% CI 1–6). Both continued to take FPV following the events.

Finally, 51 children had ALT results, of whom 32 (63%) had normal results, 15 (29%) had grade 1 results, and three (6%) grade 2 results. One HBV-co-infected child (HBsAg positive with detectable HBV DNA and/or HBeAg positive) had one grade 3 and one grade 4 result, between 12–24 months after starting FPV (overall event rate for grade 3/4 of 2 per 100 person years (95% CI 0–6)). The child continued on FPV, stopping due to virological failure over a year later.

No serious AEs considered to be causally related to FPV/r were reported. Forty-two children stopped taking FPV during follow-up; reasons for stopping were non-compliance/carer's or child's decision ($n = 12$), immunological/virological failure (13), gastrointestinal tract toxicity (2), simplified treatment available (6), resistance (1), abnormal fat redistribution (1), structured treatment interruption (1), drug unavailability (1), ART change due to entering a trial (1), and unknown (4).

With the use of sales data from IMS for the study period, it is estimated that approximately 62 kg of the oral suspension was sold in countries in this study. The median weight of children aged 6–12 years (i.e. likely to take the oral suspension) in this study was 40.4 kg. On the basis of a 40-kg child receiving the recommended dose of fosamprenavir of 18 mg/kg twice daily, the estimated cumulative exposure to the oral suspension would be 118 person years.

DISCUSSION

These findings suggest that FPV is infrequently prescribed to HIV-infected children in Europe. Contextual data from participating cohorts suggest that 3% of children in current follow-up had taken the FPV licensed dose, although this may be a slight underestimate of all FPV usage as it excludes those on unlicensed doses or children exposed during clinical trials. IMS data on oral suspension sales similarly suggest low exposure to FPV in children in Europe.

There are several potential reasons for the relatively low use of FPV in Europe. Firstly, other protease inhibitors (e.g., atazanavir) are now licensed for children for once-daily use, and atazanavir and darunavir are increasingly being used preferentially in older children. Secondly, treatment guidelines vary across Europe: recent Swedish guidelines recommend atazanavir and darunavir over lopinavir, FPV, and other protease inhibitors,[8] whereas Italian and the Paediatric European Network for the Treatment of AIDS guidelines recommend FPV as a potential first-line PI treatment for patients aged >6 years.[9,10]

This study has some limitations. Firstly, AEs were only described for periods following FPV/r initiation, and children may have had pre-existing conditions (e.g., neutropenia). Secondly, we could not discern whether AEs were attributable to FPV, or to other

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drugs in the regimen. For example, the role of ritonavir in the development of dyslipidemia has been described, as has zidovudine and lamivudine with neutropenia.[11] In addition, exposure as calculated by IMS data were only for oral suspension; the same size tablets are used for children as adults; thus, it was not possible to differentiate paediatric from adult sales volumes. Our estimates were based on the assumption that all paediatric use was in children weighing 40 kg.

However, the number and rate of grade ≥3 events were low, with no discernible trend by duration of exposure. There were an elevated number of grade 2 hypercholesterolemia events, and increased serum cholesterol has previously been described in patients treated with protease inhibitors.[12] No serious clinical AEs related to FPV/r were reported.

In summary, our results suggest that long-term licensed dose FPV-containing regimens appear to be generally well tolerated with few reported toxicities in HIV-infected children in Europe, although relatively infrequently prescribed. Any toxicities reported were consistent with the known safety profile of FPV. No serious events were reported.

CONFLICT OF INTEREST

ViiV provided funding to support this post-marketing safety study and has also provided support for a similar study with a different drug. Jeanne Pimenta is a full time employee of GlaxoSmithKline. Carlo Giaquinto received consultancy fee from ViiV and GSK and has been reimbursed for international conference attendance. All other authors declare no conflicts of interest.

KEY POINTS

- Fosamprenavir, along with low-dose ritonavir, is infrequently prescribed to children with HIV in Europe.
- Findings suggest that the long-term licensed dose is well tolerated, and few toxicities were reported.
- No serious events associated with fosamprenavir were reported.
- Prospective cohort studies that routinely collect long-term safety data can provide a robust source of information for pharmacovigilance.

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ETHICS STATEMENT

Each participating study was responsible for ensuring that ethics approval for the analysis was in place and for compliance with local and national data protection requirements.

AUTHOR CONTRIBUTIONS

Contributing cohorts (listed alphabetically by cohort name):

Collaborative HIV Paediatric Study (CHIPS), UK & Ireland (Ali Judd)
CoRISPE-cat, Spain (Antoni Noguera Julian)
Italian Register (Luisa Galli)
Madrid Cohort, Spain (Jose T. Ramos Amador)
National Study of HIV in Pregnancy and Childhood (NSHPC), UK & Ireland (Pat Tookey)
St Pierre Paediatric Cohort, Belgium (Tessa Goetghebuer)
'Victor Babes' cohort, Bucharest, Romania (Luminita Ene)

Author roles:

Ali Judd, Trinh Duong, Jeanne Pimenta, Claire Thorne and Carlo Giaquinto were responsible for the study concept and design. Trinh Duong undertook statistical analyses. Ali Judd wrote the first draft of the manuscript. Ali Judd, Luisa Galli, Tessa Goetghebuer, Luminita Ene, Antoni Noguera Julian, and Jose Tomas Ramos Amador provided data for the study. All authors participated in discussions about the design of the study. They also critically reviewed the article and approved its final version to be submitted.

REFERENCES

1. Chadwick E, *et al*. Safety and antiviral activity of fosamprenavir/ritonavir once daily regimens in HIV-infected paediatric subjects ages 2 to 18 years (48-week interim data, study APV20003). In *14th Conference on Retroviruses and Opportunistic Infections* 2007. Los Angeles.
2. Cotton M, *et al. Pharmacokinetics, safety and antiviral activity of fosamprenavir/ritonavir-containing regimens in HIV-positive four weeks to <two year-old children (48-week data, study APV20002, a prospective, open-*

label, *multi-centre*, *48-week cohort study*). In *19th International AIDS Conference* (*IAC*) 2012. Washington, DC. Abstract TUAB0202.
3. Voronin E, *et al*. Pharmacokinetics, safety and antiviral activity of fosamprenavir-containing regimens in HIV-positive 2 to 18 year-old children (48-week data, Study APV29005, a prospective, open-label, multi-centre, 48-week cohort study). in *19th International AIDS Conference* (*IAC*). 2012. Washington, DC. Abstract no. MOPE049.
4. GSK Clinical Study Register, *Available at*: http://www.gsk-clinicalstudyregister.com/index.jsp.
5. Palladino C, *et al*., Long-term efficacy and safety of fosamprenavir in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J* 2010; **29**(6): 563–566.
6. de Wolf F, *et al*., Developing a multidisciplinary network for clinical research on HIV infection: the EuroCoord experience. *Clinical Investigation* 2012; **2**: 255–264.
7. Division of AIDS, *Division of AIDS table for grading the severity of adult and pediatric adverse events*. *Version 1.0*, *December* 2004; *clarification August 2009*, Bethesda, MD: National Institutes of Health.
8. Anon, Antiretroviral treatment of HIV infection—updated Swedish recommendations 2009. Information from the Swedish Medical Product Agency, 2011; **3**: 8–35 (Article in Swedish).
9. Giaquinto C, *et al*., Italian consensus statement on paediatric HIV infection. *Infection* 2010; **38**(4): 301–319.
10. Welch S, *et al*., PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Med* 2009; **10**(10): 591–613.
11. Calmy A, *et al*., Clinical update: adverse effects of antiretroviral therapy. *Lancet* 2007; **370**(9581): 12–14.
12. Torres H.A., Arduino R.C., Fosamprenavir calcium plus ritonavir for HIV infection. *Expert Rev Anti Infect Ther* 2007; **5**(3): 349–363.