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Contraception 77 (2008) 84–90

Contraception

Original research article

Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093☆

D. Heather Watts[a,*], Jeong-Gun Park[b], Susan E. Cohn[c], Song Yu[b], Jane Hitti[d], Alice Stek[e], Pamela A. Clax[f], Laila Muderspach[e], Juan J.L. Lertora[g,1]

[a]National Institute of Child Health and Human Development, Bethesda, MD 20892, USA
[b]Harvard School of Public Health and Frontier Science and Technology Research Foundation, Boston, MA 02115, USA
[c]Department of Medicine, University of Rochester Medical Center, Rochester, NY 14642, USA
[d]Department of Obstetrics and Gynecology, University of Washington, Seattle, WA 98195, USA
[e]University of Southern California School of Medicine, Los Angeles, CA 90033, USA
[f]Medical Affairs, Pfizer Inc., New York, NY 10017, USA
[g]Tulane-LSU-Charity Hospital GCRC, Tulane University Health Sciences Center, New Orleans, LA 70112, USA

Received 24 October 2007; revised 24 October 2007; accepted 29 October 2007

Abstract

Background: Concomitant use of antiretroviral (ARV) and hormonal contraceptives may change the metabolism of each and the resulting safety profiles. We evaluated the safety and tolerability of depot medroxyprogesterone acetate (DMPA) among women on ARV.
Study Design: HIV-infected women on selected ARV regimens or no ARV were administered DMPA 150 mg intramuscularly and evaluated for 12 weeks for adverse events, changes in CD4+ count and HIV RNA levels, and ovulation.
Results: Seventy evaluable subjects were included, 16 on nucleoside only or no ARV, 21 on nelfinavir-containing regimens, 17 on efavirenz-containing regimens and 16 on nevirapine-containing regimens. Nine Grade 3 or 4 adverse events occurred in seven subjects; none were judged related to DMPA. The most common findings possibly related to DMPA were abnormal vaginal bleeding (nine, 12.7%), headache (three, 4.2%), abdominal pain, mood changes, insomnia, anorexia and fatigue, each occurring in two (2.9%) subjects. No significant changes in CD4+ count or HIV RNA levels occurred with DMPA. No evidence of ovulation was detected, and no pregnancies occurred.
Conclusions: The clinical profile associated with DMPA administration in HIV-infected women, most on ARV, appears similar to that seen in HIV-uninfected women. DMPA prevented ovulation and did not affect CD4+ counts or HIV RNA levels. In concert with previously published DMPA/ARV interaction data, these data suggest that DMPA can be used safely by HIV-infected women on the ARV studied.

Keywords: HIV; Women; Depotmedroxyprogesterone; Antiretrovirals; Contraception

1. Introduction

The proportion of AIDS cases among women continues to increase in the United States, and worldwide, women account for nearly half of HIV-infected adults [1,2]. The majority of HIV-infected women are of reproductive age, and many choose to limit the chance of pregnancy. However, data are limited on the potential interactions of hormonal contraceptives and antiretroviral (ARV) medications, limiting the contraceptive options for HIV-infected women receiving ARVs.

Depot medroxyprogesterone acetate (DMPA) given as 150 mg intramuscular injection every 3 months is a highly

☆ Juan J.L. Lertora, MD, PhD, was an investigator in protocols sponsored by Bristol Myers Squibb, Gilead and Schering. Pamela A. Clax, DPM, is an employee of Pfizer, Inc., and owns stock in Pfizer. Alice Stek, MD, is on the Pfizer speakers' bureau. Susan E. Cohn, MD, MPH, had equity interest in Pfizer, Inc., Merck and Company and Pharmacia before the start of this study. She currently has equity interest in Merck and Company, Inc.

* Corresponding author. Pediatric, Adolescent, and Maternal AIDS Branch, CRMC/NICHD/NIH, 6100 Executive Blvd., Room 4B11, MSC 7510, Bethesda, MD 20892, USA (for courier delivery, use Rockville, MD 20852). Tel.: +1 301 435 6874; fax: +1 301 496 8678.
E-mail address: wattsh@mail.nih.gov (D.H. Watts).
[1] Current address: National Institutes of Health, Bethesda, MD 20892, USA.

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doi:10.1016/j.contraception.2007.10.002

effective contraceptive agent, used by millions of women worldwide [3]. The most common side effects of its use in HIV-uninfected woman are menstrual irregularities or amenorrhea and weight gain, with headaches, abdominal discomfort, dizziness and mood changes being less common [3]. Few data exist to assess the safety and tolerability of DMPA among HIV-infected women, especially those also receiving ARV therapy. Side effects could be compounded by symptoms of HIV progression or toxicities of ARV agents such as dizziness occurring with efavirenz. The effects of initiation of DMPA on HIV RNA levels have not been evaluated, although one study demonstrated higher HIV RNA levels after initial infection among women who seroconverted to HIV-1 while on DMPA compared to those not on DMPA at seroconversion [4]. We evaluated the safety and tolerability of DMPA among HIV-infected women on a variety of ARV regimens by examining the frequency of symptoms potentially related to DMPA and assessing changes in HIV RNA levels and CD4+ cell counts.

2. Methods

AIDS Clinical Trials Group Protocol 5093 (ACTG 5093) was a 12-week, open-label, nonrandomized study of steady-state pharmacokinetic interactions between DMPA and selected ARV agents in women. More detailed methods and pharmacokinetic results have been reported previously [5]. Women were eligible for enrollment if they were on stable ARV regimens for at least 30 days containing one of three targeted drugs [nelfinavir (Pfizer, New York, NY), efavirenz (Bristol-Myers Squibb, New York, NY) or nevirapine (Boehringer Ingelheim, Ridgefield, CT), on no ARV or on a stable regimen of only nucleoside agents, and had no contraindications to receiving DMPA. Women on no ARV therapy were required to have a CD4+ cell count above 350 cells/μL consistent with current treatment guidelines, while those on ARV regimens had to have a CD4+ cell count over 200 cells/μL to minimize the risk of concomitant illnesses. The protocol was approved by the institutional review board at each participating site, and informed consent was obtained from each woman before participation. Baseline history, including recent menstrual history, and physical examination were performed. Women were classified as having abnormal menses if they reported cycles shorter than 25 days or longer than 35 days, or irregular cycles. Baseline laboratory data including complete blood count with differential, CD4+ cell counts, HIV RNA levels, liver transaminases, creatinine, amylase, bilirubin, international normalized ratio of the prothrombin time, progesterone and medroxyprogesterone levels were obtained. For women enrolled in the nelfinavir, efavirenz and nevirapine arms, serial blood draws for ARV levels were obtained over a 10-h period at baseline before DMPA administration and again four weeks after DMPA administration. A negative pregnancy test was required within 24 h before DMPA administration, which occurred within 7 days of onset of menses and more than 30 days after pregnancy. Because of the unproven efficacy of DMPA when used with ARV agents, women were required to use a second, nonhormonal method of contraception (barrier method, intrauterine device or sterilization) during the study.

Subjects received a single 150-mg DMPA injection in the gluteal region (Pfizer), at study entry. Follow-up study visits occurred 2, 4, 6, 8, 10 and 12 weeks after DMPA administration. At each visit, an interval history was obtained, including questions regarding any new symptoms or change in baseline findings and use of prescription and nonprescription medications. A targeted physical examination was performed, and blood was drawn for progesterone and medroxyprogesterone levels. HIV RNA levels were repeated at Weeks 2, 4, 8 and 12. CD4+ cell counts, complete blood counts, liver transaminases and chemistries were repeated at Weeks 4 and 12.

New symptoms, signs or laboratory abnormalities were graded using the standardized Division of AIDS (DAIDS) Table for Grading Severity of Adult Adverse Experiences©, August, 1992 http://rcc.tech-res.com/tox_tables.htm. Signs and symptoms were graded as mild, moderate, severe or life threatening, with mild symptoms usually requiring no therapy, moderate symptoms requiring no therapy or only outpatient treatment and severe symptoms requiring medical intervention and possible treatment in the hospital. All signs and symptoms of any grade and laboratory abnormalities of Grade 2 or higher were recorded on the case report forms. All adverse events reported were reviewed by the team on monthly calls and assigned causality as definitely, probably, possibly, unlikely or not treatment-related to the primary study treatment which was DMPA.

HIV RNA assays were performed in laboratories certified by the DAIDS Virology Quality Assurance Program using the Roche Ultra-sensitive or Roche RT-PCR (Amplicor, Pleasonton, CA) HIV-1 monitor assays [6]. CD4+ cell counts were performed using standard flow cytometric methods in laboratories certified by the DAIDS Quality Assurance Program [7]. Progesterone levels were measured at each visit using an enzyme-modified immunoassay. Progesterone concentrations above 5 ng/mL were considered as presumptive evidence of ovulation.

The sample size for the study was based on having 90% power to detect differences at the .05 significance level between the area under the concentration time curves for the selected ARV agents before and after DMPA administration and comparing DMPA metabolism between women on the selected ARV agents and those on no therapy or nucleoside therapy alone [5]. MPA levels were measured using high-pressure liquid chromatography–mass spectroscopy with a lower limit of detection of 0.02 ng/mL. Levels were drawn pre-dose (Week 0) and Weeks, 2, 4, 6, 8, 10 and 12. The proportion of women with HIV RNA levels below 400 copies/mL was compared between the visit weeks within each arm using a χ^2 test. A nonparametric Wilcoxon signed-