

CASE REPORT

CASO CLINICO

Stevens-Johnson syndrome and acute multi-organ hypersensitivity syndrome due to lopinavir administration

Sindrome di Stevens-Johnson e sindrome acuta da ipersensibilità a coinvolgimento multi-organo dopo somministrazione di lopinavir

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Key words

Lopinavir • Acute hypersensitivity reaction • Stevens-Johnson syndrome • Myelotoxicity • Liver and kidney toxicity

Parole chiave

Lopinavir • Reazione acuta di ipersensibilità • Sindrome di Stevens-Johnson • Mielotossicità • Tossicità epatica e renale

Summary

A severe hypersensitivity reaction occurred in a multi-experienced, immunocompromised HIV-infected patient a few days after switching the highly active antiretroviral therapy (HAART) towards a lopinavir-containing regimen. The serious cutaneous-mucous rash (a Stevens-Johnson-like syndrome), associated with transient, but severe myelotoxicity and liver and kidney failure, was related to lopinavir alone, since all other concurrent medications (including full-dose and low-dose ritonavir), were previously taken by our patient without any toxicity sign or symptom, and no toxicity occurred upon restarting HAART (rechallenge) with an atazanavir/ritonavir-based combination. This very rare, acute and serious lopinavir intolerance should draw our attention on the possible short-term toxicity of protease inhibitors, as opposed to the well-known and expected long-term intolerance.

Riassunto

Una grave reazione di ipersensibilità acuta è stata osservata in una paziente con infezione da HIV immunocompromessa e sottoposta in passato a molteplici e prolungate terapie antiretrovirali, pochi giorni dopo aver modificato il regime di highly active antiretroviral therapy (HAART) con l'introduzione di lopinavir-ritonavir. La severa eruzione cutaneo-mucosa di tipo eritemato-desquamativo (ricongducibile ad un quadro di sindrome di Stevens-Johnson), associata alla comparsa di transitoria, ma grave, mielotossicità ed insufficienza epatica e renale, risultava correlabile al solo lopinavir, in quanto tutti gli altri medicinali contemporaneamente somministrati (ivi compreso ritonavir a dose piena e a dose di booster), erano stati assunti nel passato dalla nostra paziente senza alcun segno o sintomo di tossicità, e nessun evento indesiderato si è manifestato in occasione della ripresa dell'HAART (rechallenge), con un regime basato su atazanavir/ritonavir. Questo raro episodio di acuta e severa intolleranza al lopinavir porta l'attenzione dei clinici sulla possibile tossicità a breve termine degli inibitori della proteasi, rispetto ai ben noti ed attesi effetti indesiderati indotti da questa classe di farmaci sul lungo periodo.

Introduction

Compared with that of the other three available antiretroviral classes (nucleoside-nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and fusion inhibitors), protease inhibitor-related toxicity appears mainly related to a broad spectrum of long-term side effects responsible for a varied and sometimes associated clinical and

laboratory presentations, and linked to a series of different pathogenetic pathways¹⁻⁵.

An exemplary case report of an unexpected, serious, rapid-onset reaction to lopinavir administration occurred in a largely antiretroviral-experienced patient with HIV-related immunodeficiency, underlines the importance to report and take into maximum consideration also short-term multi-organ toxicity associated with protease inhibitors.

Case report

A 38-year-old woman with HIV infection discovered since seven years, immediately underwent HAART due to an already severe immunodeficiency (as expressed by a CD4+ lymphocyte count of 102 cells/ μ L), and an elevated HIV viral load (89,000 copies/mL). Although no concurrent illnesses (including viral hepatitis) were present, an insufficient highly active antiretroviral therapy (HAART) adherence, a limited immune system recovery, the progressive development of HIV genotypic resistances, and some, different adverse events occurring over time, prompted even eleven changes of HAART until Summer, 2006. When considering in particular previously administered protease inhibitors, non-boosterized indinavir was interrupted after seven months due to suspected kidney colics, full-dose ritonavir was suspended after 16 months due to poor compliance, an indinavir-ritonavir combination was withdrawn after 13 months due to genotypic resistance, as well as a subsequent 11-month course of nelfinavir.

Twelve weeks ago our patient developed an AIDS-defining esophageal candidiasis associated with hyperpyrexia, toxemia, and weight loss. HAART was spontaneously interrupted by our patient shortly before hospitalization, when her CD4+ lymphocyte count was 58 cells/ μ L, and the viral load was 58,000 HIV-RNA copies/mL. Three weeks after treating successfully the mycotic opportunistic infection with a well-tolerated fluconazole course, and after excluding other HIV-related and HIV-unrelated concurrent illnesses, an HAART regimen was re-started on the ground of the last genotypization testing, which suggested a lamivudine-stavudine-lopinavir/ritonavir combination. All the remaining pharmacotherapies (including fluconazole and atovaquone, for opportunism prophylaxis), were left unchanged, while no relevant laboratory abnormalities of liver and kidney function and myelopoiesis were present.

Five days after the introduction of this last HAART combination, a sudden and severe cutaneous-mucous hypersensitivity reaction occurred, characterized by a diffuse, maculo-papular and orticarioid rash accompanied by intense itching and hyperpyrexia, and a severe enanthema associated with multiple and painful mucosal ulcerations of the mouth and pharynx (leading to a diagnosis of Stevens-Johnson syndrome). One day after, an unexpected hepatotoxicity appeared, as represented by an over three-fold increase of serum transaminases, moderately increased serum bilirubin, gamma-GT, alkaline phosphatase, and lactic dehydrogenase levels, a severe serum cholinesterase deficiency (1.5 ku/L; normal range for females 4.3-11.2 ku/L), and a reduced serum albumin (2.2 g/dL), the last one leading to the development of extensive limb and face edema. A sudden drop of total leukocyte count was

also observed (1,810 cells/ μ L), with a proportionally increased eosinophil rate (13%), and anemia (hemoglobin 8.1 g/dL), and thrombocytopenia (platelets 61,000/ μ L) became also apparent (as compared with the normal pre-HAART values). In the next two days, despite immediate HAART withdrawal and corticosteroid, antihistaminic, and an extensive supportive treatment, kidney function abnormalities occurred, including oliguria (minimum output 600 mL/day), a moderately increased serum creatinine level (1.47 mg/dL), and especially generalized electrolyte imbalances (serum potassium 2.5 mEq/L, serum magnesium 1.2 mg/dL, serum calcium 7.4 mg/dL), accompanied by a tubular kidney dysfunction characterized by a persisting, extremely low urine concentration (1,002). Slight-to-moderate abnormalities of serum clotting tests were also observed in the same period.

Only during the subsequent week of intensive, supportive monitoring and care including a careful fluid-electrolyte management, continued i.v. steroid and daily albumin administration, and repeated erythrocyte transfusions, the skin and mucous rash slowly evolved into a generalized, desquamative phase with epidermal detachment (very intense at both face and limbs, and oropharynx), after the rapid formation and disappearance of several blister and bullous lesions. On the other hand, repeated laboratory examinations showed a progressive normalization of all altered liver, kidney, and myelopoietic parameters, which became almost complete two weeks after HAART interruption, and did not show any relapse and/or sequelae during the subsequent follow-up, and also after that a novel atazanavir/ritonavir-based HAART was administered (two weeks later), and well tolerated until now (10 subsequent weeks of outpatient follow-up).

Discussion

In our unique case report, the patient's clinical history allows us to exclude a prior hypersensitivity to drugs co-administered with HAART, since antimicrobials like fluconazole and atovaquone were taken for a long time in the past, and continued during the last admission. Moreover, lamivudine and stavudine have been administered for a very long time (48 and 36 months, respectively), during previous HAART lines. The HAART re-introduction was also retarded of three weeks after fluconazole therapy for esophageal candidiasis, in order to avoid a possible immune reconstitution syndrome, described when treating an underlying opportunistic infection in patients with very low CD4+ lymphocyte counts⁶.

As a whole, the fixed combination of lopinavir and ritonavir is largely known as a safe and well tolerated compound, and is widely used as a first-line protease

inhibitor combination due to its extensive potency and very favorable resistance profile^{1,5}. Importantly, among the different available protease inhibitors, in the presented case we can narrow our attention on lopinavir only, since indinavir, nelfinavir, atazanavir, and especially ritonavir (either full-dose ritonavir taken in the past, and booster ritonavir dosages used together indinavir, and atazanavir after the present episode), never generated adverse events, save the six-year-old suspected renal colics while our patient was on an indinavir-based HAART.

An hyperacute and severe skin and mucous hypersensitivity reaction compatible with a diagnosis of Stevens-Johnson syndrome has been reported in less than 1% of HIV-infected patients treated with non-nucleoside reverse transcriptase inhibitors, usually female patients with a CD4+ lymphocyte count above 250 cells/ μ L^{7,8}, and in single, anecdotal, or on-file cases of subjects receiving abacavir, other nucleoside analogues, and indinavir, fosamprenavir, atazanavir, and lopinavir/ritonavir, too, among protease inhibitors², although in these last reports no extensive details were given with respect to concomitant medications, clinical evolution and outcome, and eventual drug rechallenges^{1,2,5}. A pruritic maculopapular rash has been reported in two Italian patients 7-10 days after initiation of lopinavir/ritonavir⁹. In this clinical report, the clinical picture improved on withdrawal, and relapsed upon rechallenge with the same protease inhibitor combination, although the drugs were not interrupted, since a supportive antihistaminic therapy allowed lopinavir/ritonavir continuation⁹. Curiously, the only remaining report of an "acute generalized exanthematous pustulosis" was described during a post-exposure prophylaxis conducted with a lopinavir/ritonavir-based regimen, in a HIV-negative subject¹⁰. Bone marrow suppression was not apparently linked with any protease inhibitor², and lopinavir too⁵, but the multi-organ failure showed by our patient also prompted this unexpected myelotoxicity.

On the other hand, a mild-to-moderate protease inhibitor-associated hepatotoxicity is a quite common, but self-limiting phenomenon, usually exacerbated by concurrent viral hepatitis, chronic hepato-biliary disorders, and/or other co-administered medications^{2,4,5}. However, our patient showed a very severe decrease of hepatic function, as demonstrated by a significantly reduced serum cholinesterase activity compared with baseline levels. Finally, nephrotoxicity is a well known side effect of either indinavir- or tenofovir-containing regimens, but it never involved lopinavir-treated patients, as far as we know^{1,4,5,11,12}, but could be part of the multi-organ involvement occurred in our patients who experienced a broad-spectrum end-organ lopinavir hypersensitivity and toxicity. On the ground of the available literature data, in an extensive study of hepatotoxicity of protease inhibitor-based HAART, the incidence of grade 3-4 elevation of serum transaminases among protease inhibitor-naïve patients was estimated to be only 9% for lopinavir/ritonavir (the lowest in the class)⁴. In fact, a reduced incidence of liver toxicity is also reported by the lopinavir/ritonavir product labelling, while no reference to severe skin hypersensitivity, myelotoxicity, and kidney failure is mentioned^{13,14,15-17}. Moreover, very poor toxicology informations are available regarding lopinavir alone (when excluding preliminary studies)^{4,13,15,17}, while in our case we had the possibility to exclude with very reasonable certainty a responsibility for the co-formulated ritonavir booster.

To conclude, our exceptional report of a combined, severe skin and mucous hypersensitivity reaction resembling a Stevens-Johnson syndrome, associated with a transient but serious hepatic and kidney failure and myelotoxicity, does not have analogues until now, and although infrequent it represents a warning for Clinicians engaged in the management of HIV disease to be extremely cautious also with short-term, infrequent and unexpected adverse events which can occur shortly after the introduction of a novel protease inhibitor, like lopinavir in our case.

References

- Cvetkovic RS, Goa KL. *Lopinavir/ritonavir: a review of its use in the management of HIV infection*. *Drugs* 2003;63:769-802.
- DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC). *Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents*. Available on the world wide web from May 4, 2006, at <http://AIDSinfo.nih.gov>:1-112.
- Manfredi R. *HIV infection, antiretroviral therapy, and hepatic function. Emerging epidemiological, pathogenetic, and clinical issues, and their consequences on disease management*. *AIDS* 2003;17:2253-6.
- Sulkowski MS, Metha SH, Chaisson RE, Thomas DL, Moore RD. *Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir*. *AIDS* 2004;18:2277-84.
- Vogel M, Rocksroh JK. *Safety of lopinavir/ritonavir for the treatment of HIV-infection*. *Expert Opin Drug Saf* 2005;4:403-20.
- Manfredi R, Pieri F, Pileri SA, Chiodo F. *The changing face of AIDS-related opportunism: cryptococcosis in the highly active antiretroviral therapy (HAART) era. Case reports and literature review*. *Mycopathologia* 1999;148:73-8.
- Colebunders R, Vanwolleghem T, Meurrens P, Moerman F. *Efavirenz-associated Stevens-Johnson syndrome*. *Infection* 2004;32:306-7.

- ⁸ Liechty CA, Solberg P, Mwima G, Were W, Weidle PJ, Mermin J. *Nevirapine-induced Stevens-Johnson syndrome in a mother and son*. AIDS 2005;19:993-4.
- ⁹ Calista D. *Maculo-papular rash induced by lopinavir/ritonavir*. Eur J Dermatol 2005;15:97-8.
- ¹⁰ Ghosn J, Duvivier C, Tubiana R, Katlama C, Caumes E. *Acute generalized exanthematous pustolosis induced by HIV postexposure prophylaxis with lopinavir/ritonavir*. Clin Infect Dis 2005;41:1360-1.
- ¹¹ Cho ME, Kopp JB. *HIV and the kidney: a status report after 20 years*. Curr HIV/AIDS Rep 2004;1:109-15.
- ¹² Szeto CC, Chow KM. *Nephrotoxicity related to new therapeutic compounds*. Ren Fail 2005;27:329-33.
- ¹³ Corbett AH, Lim ML, Kashuba AD. *Kaletra (lopinavir/ritonavir)*. Ann Pharmacother 2002;36:1193-203.
- ¹⁴ Kaletra product labelling, last available update. Abbott Italy, January 2006.
- ¹⁵ Mangum EM, Graham KK. *Lopinavir-ritonavir: a new protease inhibitor*. Pharmacotherapy 2001;21:1352-63.
- ¹⁶ Murphy RL, Brun S, Hicks C. *ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naïve adults with HIV-1 infection: 48-week results*. AIDS 2001;15: F1-F9.
- ¹⁷ Qazi NA, Moriese JF, Pozniak AL. *Lopinavir-ritonavir (ABT-378/r)*. Expert Opin Pharmacother 2002;3:315-37.