Atazanavir and Acid-Lowering Therapy

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ABSTRACT

Background: Drug interactions represent a major problem associated with highly active antiretroviral therapy. In pharmacokinetic studies, the oral absorption of atazanavir has been compromised in low pH environments. The manufacturer of this drug recommends avoiding its use with proton pump inhibitors (PPIs) and also suggests separating its administration from that of shorter-acting acid-lowering agents, such as antacids and histamine-2 receptor antagonists.

Objective: To qualitatively review the evidence for drug interactions between atazanavir and acid-lowering therapies.

Methods: A literature search of the following databases was conducted: EMBASE (January 1980 to June 2007), MEDLINE (January 1966 to June 2007), and PubMed (January 1949 to June 2007). All prospective or retrospective studies, case series, and case reports published in English that evaluated the interaction between acid-lowering agents and atazanavir were included.

Results: Fourteen published articles fit the inclusion criteria. The results of studies of healthy adults provided evidence of an interaction between atazanavir and acid-lowering agents. However, case reports and prospective analyses in HIV-infected patients yielded conflicting results.

Conclusion: Further studies are required to establish the clinical relevance of the potential interaction between PPIs and atazanavir. Until then, the concurrent use of PPIs and atazanavir should be avoided. Alternatives include switching to an antiretroviral regimen that does not include atazanavir or using shorter-acting acid-lowering agents, such as histamine-2 antagonists and antacids, with doses administered at different times from atazanavir. If the combination of PPIs and atazanavir must be used, patients should be monitored closely for viral and immunologic failure.

Key words: atazanavir, acid-lowering therapy, proton pump inhibitors

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RÉSUMÉ

Historique : Les interactions médicamenteuses constituent un problème majeur de la multithérapie antirétrovirale. Des études pharmacocinétiques ont montré que l'absorption orale de l'atazanavir était compromise en présence d'un pH gastrique faible. Son fabricant déconseille son utilisation avec des inhibiteurs de la pompe à protons (IPP) et recommande de ne pas l'administrer simultanément avec des agents réducteurs de l'acidité gastrique d'action plus brève, comme les antiacides et les antagonistes des récepteurs H2 de l'histamine.

Objectif : Évaluer qualitativement les données probantes sur les interactions médicamenteuses entre l'atazanavir et les agents réducteurs de l'acidité gastrique.

Méthodes : Une recherche bibliographique dans les bases de données suivantes a été effectuée : EMBASE (de janvier 1980 à juin 2007), MEDLINE (de janvier 1966 à juin 2007) et PubMed (de janvier 1949 à juin 2007). Toutes les études prospectives et rétrospectives, les séries de cas et les observations cliniques publiées en anglais qui ont évalué les interactions entre les agents réducteurs de l'acidité gastrique et l'atazanavir ont été incluses.

Résultats : En tout, 14 articles publiés ont satisfait aux critères d'inclusion. Les résultats des études menées chez des adultes en bonne santé ont mis en évidence une interaction entre l'atazanavir et les agents réducteurs de l'acidité gastrique. Cependant, les observations cliniques et les analyses prospectives menées chez des patients séropositifs pour le VIH ont donné des résultats contradictoires.

Conclusion : D'autres études sont nécessaires pour établir la preuve clinique d'une interaction potentielle entre les IPP et l'atazanavir. D'ici là, l'emploi concomitant d'IPP et d'atazanavir n'est pas recommandé. Les solutions de rechange comprennent l'emploi d'une multithérapie antirétrovirale ne comportant pas d'atazanavir ou l'administration d'agents réducteurs de l'acidité gastrique d'action plus brève, comme les antagonistes des récepteurs H2 de l'histamine et les antiacides, à des heures différentes de l'atazanavir. Si on n'a d'autre choix que d'administrer des IPP et de l'atazanavir, il faut alors surveiller étroitement les patients pour l'apparition d'un échec virologique ou immunologique.

Mots clés : atazanavir, agents réducteurs de l'acidité gastrique, inhibiteurs de la pompe à protons

INTRODUCTION

The advent of highly active antiretroviral therapy has improved long-term outcomes for patients infected with HIV, but its use brings many therapeutic challenges. Drug interactions play a predominant role in these challenges and are a constant concern. Concurrent prescription drug therapies and self-medication with nonprescription agents both contribute to the complexity of these therapeutic regimens. Pharmacists must be aware of these factors and should help in identifying potential drug interactions to minimize adverse outcomes in patients.

Atazanavir is a protease inhibitor used in combination with other antiretroviral agents to treat HIV-1 infection.[1] The advantages of atazanavir over other protease inhibitors include once-daily administration and minimal adverse effects on lipid levels.[1] The bioavailability of atazanavir is pH dependent, with greater absorption in acidic environments.[2] HIV-infected patients often receive concomitant acid-lowering therapy, usually to address adverse events related to antiretroviral therapy.[3] In one survey, 88% of HIV-infected patients had received a proton pump inhibitor (PPI), a histamine-2 (H2) receptor antagonist, or an antacid since starting HIV therapy.[3] The manufacturer of atazanavir (Reyataz), Bristol-Myers Squibb, recommends avoiding concomitant use of PPIs, administering antacids or buffered medications at least 1 h before or 2 h after atazanavir, and administering H2 receptor antagonists at least 10 h before or 2 h after atazanavir.[4] Despite these recommendations, it is not always possible to avoid concomitant use of atazanavir and acid-lowering therapies. In cases where the use of both is unavoidable, it is important for clinicians to understand the evidence behind the manufacturer's recommendations, so they can evaluate for particular patients the clinical relevance of any potential drug interaction.

This article documents a qualitative review of the literature regarding recently documented drug interactions between atazanavir and acid-lowering agents, including PPIs, H2 receptor antagonists, and other antacids.

METHODS

A search of the following databases was conducted: EMBASE (January 1980 to June 2007), MEDLINE (January 1966 to June 2007), and PubMed (January 1949 to June 2007). The following search terms were used: "atazanavir", "proton pump inhibitors", "H2 antagonists", "antacids", and "drug interactions". The reference lists for all retrieved articles were also manually reviewed. Studies were included if they were retrospective or prospective and published either in full or as abstracts. Case series and case reports were also included. Studies were excluded if they were published in languages other than English. Both authors were involved in applying the criteria to the retrieved articles, and disagreements were resolved by discussion.

RESULTS

The search yielded 200 articles, but only 14 met the inclusion criteria (Table 1): 1 prospective study conducted in HIV-positive patients,[5] 5 prospective studies conducted in healthy volunteers,[6-10] 4 chart reviews involving HIV-positive patients,[11-14] and 4 case reports.[15-18]

Prospective Studies

Only 1 prospective trial evaluating HIV-infected individuals has been published to date.[5] Ninety-two patients were enrolled in this prospective open-label study comparing plasma trough concentrations (C_{min}) of atazanavir in HIV-infected patients receiving this drug 300 mg with ritonavir 100 mg daily with or without a PPI. Patients were interviewed after undergoing at least 1 week of antiretroviral therapy to determine whether they were taking any acid-lowering therapy and the timing of their most recent dose of atazanavir and ritonavir. Only C_{min} values measured 24 ± 4 h after the most recent doses were evaluated. A total of 13 patients were taking a PPI. Of these, 9 were taking omeprazole 20 mg daily, 1 was taking omeprazole 40 mg daily, and 3 were taking rabeprazole 20 mg daily. No difference in the median plasma atazanavir C_{min} was observed between the 13 patients taking a PPI (median 551 ng/mL, range 203–1976 ng/mL) and the 79 patients not taking a PPI (median 469 ng/mL, range 65–1944 ng/mL) (p = 0.86). The authors did not report whether patient compliance with prescribed therapy was assessed.

Agarwala and others[6-8] have presented 3 abstracts evaluating the effects of acid-lowering agents on the pharmacokinetics of atazanavir in healthy subjects. In one abstract, Agarwala and others[7] reported the effects of famotidine 40 mg twice daily on the pharmacokinetics of atazanavir in the presence and absence of ritonavir. In the first part of this study, healthy adults were given atazanavir 400 mg daily for 6 days and then were randomly assigned to 1 of 4 treatment arms (n = 16 for each arm): atazanavir 400 mg daily and famotidine for 6 days; atazanavir 400 mg daily, famotidine, and cola for 6 days; atazanavir 400 mg daily, administered 10 h from the morning famotidine dose and 2 h from the evening

Table 1. Studies Included in an Analysis of Potential Interactions between Atanazavir and Acid-Lowering Agents

Reference	Subjects	Acid-Lowering Agent(s)	Supports or Refutes Drug Interaction	
			Pharmacokinetic Interaction	Clinically Relevant Interaction
Prospective, open-label studies				
Guiard-Schmid et al.[5]	92 HIV patients receiving atazanavir 300 mg/day and ritonavir 100 mg/day without (*n* = 79) or with (*n* = 13) PPI	PPI: omeprazole 20 or 40 mg/day (*n* = 10) or rabeprazole 20 mg/day (*n* = 3)	Refutes	NA
Agarwala et al.[6]	Healthy volunteers (*n* = 48) receiving atazanavir 300 or 400 mg/day + ritonavir 100 mg/day with PPI, with or without cola	PPI: omeprazole 40 mg/day	Supports	NA
Prospective, randomized, open-label studies				
Agarwala et al.[7], part 1	Healthy volunteers (*n* = 64) receiving famotidine and randomized to 1 of 4 treatment arms (atazanavir 400 mg/day; atazanavir 400 mg/day + cola; atazanavir 400 mg/day temporally separated from famotidine; atazanavir 300 mg/day + ritonavir 100 mg/day)	Famotidine 40 mg bid	Supports when famotidine and atazanavir administered simultaneously; refutes when doses of famotidine and atazanavir spaced temporally	NA
Agarwala et al.[7], part 2	Healthy volunteers (*n* = 48) receiving famotidine and randomized to 1 of 3 treatment arms (atazanavir 300 mg/day + ritonavir 100 mg/day; atazanavir 300 mg/day + ritonavir 100 mg/day + cola; atazanavir 400 mg/day + ritonavir 100 mg/day)	Famotidine 40 mg bid	Supports when famotidine administered with atazanavir and ritonavir; AUC and C_{min} values maintained with higher doses of atazanavir (400 mg) or ritonavir (100 mg)	NA
Agarwala et al.[8]	Healthy volunteers (*n* = 48) receiving omeprazole PLUS one of the following: atazanavir 400 mg/day OR atazanavir 400 mg/day with cola OR atazanavir 300 mg/day + ritonavir 100 mg/day	PPI: omeprazole 40 mg (given 2 h before atazanavir or ritonavir)	Supports	NA
Prospective, open-label, crossover studies				
Luber et al.[9]	Healthy volunteers (*n* = 19) receiving atazanavir 300 mg/day with ritonavir 100 mg/day (given in the morning) with or without PPI	PPI: omeprazole 20 mg/day, given in the evening	Supports	NA
Tomilo et al.[10]*	Healthy volunteers (*n* = 10) receiving a single dose of atazanavir 400 mg (with or without lansoprazole)	PPI: lansoprazole 60 mg (2 doses)	Supports	NA

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Table 1. continued

Reference	Subjects	Acid-Lowering Agent(s)	Supports or Refutes Drug Interaction	
			Pharmacokinetic Interaction	Clinically Relevant Interaction
Chart reviews				
Khanlou and Farthing[11]	HIV patients (*n* = 34) receiving atazanavir + PPI or H2 receptor antagonist	PPI (*n* = 15) or H2 receptor antagonist (*n* = 19)	Supports	Supports
Antoniou et al.[12]	HIV patients receiving atazanavir (for ≥ 4 weeks) + PPI or H2 receptor antagonist regularly (*n* = 14)	PPI: lansoprazole 30 mg/day, omeprazole 20 mg/day, pantoprazole 40 mg/day, esomeprazole 20 mg/day H2 receptor antagonist: ranitidine 150 mg/day Other: didanosine buffered tablets	NA	Refutes
Sahloff and Duggan[13]	HIV-infected patients (median age 38 years) (*n* = 12) receiving atazanavir (with or without ritonavir) + PPI	PPI: lansoprazole 20–30 mg/day, omeprazole 20 mg/day, rabeprazole 20 mg/day, esomeprazole 40 mg/day	NA	Refutes
Furtek et al.[14]	HIV-infected patients receiving atazanavir + PPI for ≥ 6 weeks (*n* = 10)	PPI: omeprazole 20 mg/day or rabeprazole 20 or 40 mg/day	NA	Refutes
Case reports				
Kiser et al.[15]	65-year-old white HIV-infected man (CD4 = 180/mm^3 [10%]; HIV RNA = 9360 copies/mL) receiving atazanavir 300 mg/day, ritonavir 100 mg/day, tenofovir 300 mg/day, stavudine 30 mg bid	PPI: esomeprazole 40 mg/day	Supports	NA
Kosel et al.[16]	40-year-old HIV-infected man receiving atazanavir 300 mg/day, ritonavir 100 mg/day, tenofovir 300 mg/day, lamivudine 300 mg/day	PPI: lansoprazole 30 mg bid (for GERD and Barrett's esophagitis) before starting antiretroviral therapy; ranitidine 300 mg/day (separated from antiretroviral therapy by 12 h) for 1 month when starting atazanavir, then switched back to lansoprazole 30 mg bid	Refutes	Refutes
Chan-Tack and Edozien[17]	50-year-old African-American man (CD4 = 1095 cells/mm^3 [23%]; HIV RNA = 88 copies/mL) receiving stavudine, lamivudine, and atazanavir	PPI: omeprazole 20 mg/day	NA	Refutes
Goicoechea et al.[18]	56-year-old HIV-infected man (CD4 = 494 cells/mm^3; HIV RNA = 64 800 copies/mL) receiving atazanavir, ritonavir, tenofovir, abacavir, lamivudine	PPI: omeprazole 40 mg/day	Supports	Refutes

PPI = proton-pump inhibitor, NA = not applicable, AUC = area under the curve, C_{min} = minimum concentration, GERD = gastroesophageal reflux disease.
*Single dose.

famotidine dose for 6 days; or atazanavir 300 mg daily, ritonavir 100 mg daily, and famotidine for 10 days. Other than in the third treatment group, atazanavir and famotidine were administered at the same time. In the second part of the study, healthy subjects were given atazanavir 300 mg and ritonavir 100 mg daily for 10 days and then were randomly assigned to 1 of 3 treatment groups (n = 16 for each arm): atazanavir 300 mg with ritonavir 100 mg daily and famotidine; atazanavir 300 mg with ritonavir 100 mg daily, famotidine, and cola; or atazanavir 400 mg with ritonavir 100 mg daily and famotidine. All doses of famotidine were coadministered with atazanavir. Treatment was continued for 10 days in each arm. In the first part of the study, the area under the curve (AUC) for atazanavir decreased to 41% and C_{min} decreased to 42% of their original values when famotidine was added; the investigators did not indicate whether these decreases were statistically significant. When the administration of famotidine was temporally spaced from the administration of atazanavir, the AUC and C_{min} values were similar to those obtained with atazanavir 400 mg daily alone. In the second part of the study, when pharmacokinetic values were compared with those for subjects who received atazanavir 300 mg with ritonavir 100 mg daily, the addition of famotidine reduced the AUC for atazanavir to 18% and the C_{min} to 28% of their original values. As before, the investigators did not indicate whether these decreases were statistically significant. When famotidine was added to a higher dose of atazanavir (400 mg daily) given with ritonavir 100 mg daily, the AUC and C_{min} values were similar to those obtained with atazanavir 300 mg daily plus ritonavir 100 mg daily. In both parts of this study, the addition of cola did not mitigate the pharmacokinetic effects of famotidine on atazanavir.

The second abstract, presented in 2005 by Agarwala and others,[8] described the pharmacokinetic interaction between atazanavir and omeprazole. Forty-eight healthy subjects received atazanavir 400 mg daily for 6 days and were then randomly assigned to receive either atazanavir 400 mg plus omeprazole 40 mg daily for 6 days; atazanavir 400 mg and omeprazole 40 mg daily with cola for 6 days; or atazanavir 300 mg with ritonavir 100 mg daily and omeprazole 40 mg daily for 10 days. For the subjects who received atazanavir without ritonavir or cola, the omeprazole was given 2 h after the dose of atazanavir on the first day of the study only. The ratios of the geometric means (90% confidence intervals [CIs]) for the comparison between subjects who received atazanavir 400 mg and omeprazole 40 mg daily (for 6 days) and those who received only atazanavir 400 mg daily (also for 6 days) were 0.06 (0.05–0.07) for AUC and 0.05 (0.03–0.07) for C_{min}, corresponding to a 94% reduction in AUC and a 95% reduction in C_{min}. The ratios of the geometric means (90% CIs) for the comparison between subjects who received atazanavir 300 mg with ritonavir 100 mg daily and omeprazole 40 mg daily (for 10 days) and those who received only atazanavir 400 mg daily (for 6 days) were 0.50 (0.42–0.60) for AUC and 1.23 (1.00–1.52) for C_{min}, corresponding to a 50% reduction in AUC and a 23% increase in C_{min}.

A third abstract by the same group described the pharmacokinetic effect of omeprazole on patients receiving atazanavir coadministered with ritonavir.[6] Forty-eight healthy subjects received atazanavir 300 mg with ritonavir 100 mg daily for 10 days. The subjects were then randomly assigned to receive either atazanavir 300 mg with ritonavir 100 mg and omeprazole 40 mg daily (n = 16); atazanavir 300 mg with ritonavir 100 mg daily, omeprazole 40 mg daily, and cola (n = 16); or atazanavir 400 mg with ritonavir 100 mg and omeprazole 40 mg daily (n = 16) for the next 10 days. The omeprazole was administered in the morning, after the patient had fasted and 2 h before the atazanavir and ritonavir. Serial blood samples were collected on days 10 and 20. All three arms showed a decrease in atazanavir exposure when omeprazole was added, as indicated by the maximum concentration (C_{max}), the AUC, and C_{min}. The ratios of the geometric means (90% CIs) for the subjects who received atazanavir 300 mg with ritonavir 100 mg and omeprazole 40 mg daily were 0.28 (0.24–0.32) for C_{max}, 0.24 (0.21–0.27) for AUC, and 0.21 (0.18–0.25) for C_{min}. For the subjects who received atazanavir 300 mg with ritonavir 100 mg daily, omeprazole 40 mg daily, and cola, the ratios of geometric means (90% CIs) were 0.34 (0.29–0.39) for C_{max}, 0.30 (0.27–0.34) for AUC, and 0.24 (0.20–0.29) for C_{min}. For the group who received atazanavir 400 mg with ritonavir 100 mg and omeprazole 40 mg daily, the ratios of geometric means (90% CIs) were 0.44 (0.38–0.51) for C_{max}, 0.39 (0.35–0.45) for AUC, and 0.31 (0.26–0.37) for C_{min}.

Another study, presented in abstract form by Luber and others,[9] involved 19 healthy adult volunteers who were given atazanavir 300 mg with ritonavir 100 mg daily in the morning alone or in combination with omeprazole 20 mg daily, the latter being given in the evening. Pharmacokinetic analysis was performed before and 7 days after initiation of omeprazole. The pharmacokinetics of atazanavir were affected as follows: C_{min} was reduced by 27%, C_{max} was reduced by 33%, and the $AUC_{0-24\ h}$ was reduced by 27%. The statistical significance of the results was not reported.[9]

In a single-dose, open-label, 2-phase, crossover study involving 10 healthy adults, Tomilo and others[10] investigated the effect of lansoprazole 60 mg on the pharmacokinetics of atazanavir 400 mg. In the first phase of the study, serum concentrations of atazanavir were measured after a single oral dose of 400 mg. In the second phase, subjects received 2 doses of lansoprazole, on the day before and the day of sample collection when a single oral dose of atazanavir 400 mg was given. For 9 of the 10 subjects, 12 sequential blood samples were collected during the 24-h period after drug administration. The pharmacokinetic parameters measured included C_{max}, time at maximum concentration (T_{max}), $AUC_{0\text{-}24\ h}$, and half-life. Between the first and second phases of the study, there was a 94% reduction in $AUC_{0\text{-}24\ h}$ ($p < 0.01$) and a 91% reduction in C_{max} ($p < 0.01$). There was no significant change in T_{max}, and half-life could not be reliably assessed.

Retrospective Studies

A survey of 10 HIV clinics in Los Angeles identified 50 patients who were being treated with atazanavir and either a PPI or an H2 receptor antagonist.[11] Trough concentrations of atazanavir were available for 34 of the patients (15 receiving a PPI and 19 receiving an H2 receptor antagonist). For the patients receiving a PPI, the mean CD4 count was 267 cells/mm^3, and 2 patients (13%) had a viral load of less than 50 copies/mL. For the patients receiving H2 receptor antagonists, the mean CD4 count was 400 cells/mm^3, and 3 patients (16%) had a viral load less than 50 copies/mL. The mean trough concentration of the atazanavir among the 15 patients receiving a PPI was lower than that among the 19 patients receiving an H2 receptor antagonist (0.65 versus 1.12 µg/mL; p value not reported). The mean atazanavir concentrations achieved with different dosing regimens were not reported.

Using a chart review, Antoniou and others[12] attempted to determine the clinical impact of acid-lowering therapy on virologic response in antiretroviral-experienced patients receiving atazanavir-containing regimens. Fifteen patients who had been receiving atazanavir for a minimum of 4 weeks concomitantly with a PPI or an H2 receptor antagonist were included, but only 14 of them had adequate documentation for evaluation. Thirteen of the patients were men, and the median age of all patients was 51.5 years (range 38–68 years). Before initiation of an atazanavir-containing regimen, patients in this cohort had received a median of 3 highly active antiretroviral therapy regimens (range 1–8) over a median of 6.5 years (range 1–9 years). Seven of the patients had a baseline viral load of less than 50 copies/mL. Given that some patients had undetectable viral loads at baseline, it is important to note that in each of these patients, the atazanavir was being used to replace another antiretroviral agent in the context of full viral suppression. Four of the patients were receiving tenofovir, which can also reduce atazanavir levels. Eight of the patients were receiving atazanavir 300 mg boosted with ritonavir 100 mg once daily. Ten patients were taking a PPI, including lansoprazole, omeprazole, pantoprazole, or esomeprazole. Three patients were receiving ranitidine. At last follow-up, 12 of the patients had undetectable viral loads; the duration of follow-up ranged from 8 to 76 weeks.

The effect of concomitant use of atazanavir and PPIs was further explored in a chart review of 301 HIV-positive patients.[13] Patients included in the relevant analysis were older than 18 years of age and were receiving atazanavir, either alone or in combination with ritonavir, and a PPI. Twelve adults, 6 of whom were female, were identified as meeting the inclusion criteria. The median age was 38 years (range 25–60 years). Seven of the patients had previous treatment experience with protease inhibitors, and 4 had a viral load less than 400 copies/mL at baseline. The PPIs used and their dosing regimens varied among the patients. In total, 9 subjects had undetectable viral loads (less than 400 copies/mL), with durations of concurrent therapy ranging from 4 to 23 months.

Furtek and others[14] conducted a chart review for patients receiving atazanavir-containing regimens, comparing the virological responses of those taking concomitant PPI therapy and those not receiving PPIs. Of the 76 patients who were receiving atazanavir, as identified by pharmacy records, only 10 were receiving concomitant PPI treatment: 8 patients received rabeprazole 20 mg daily, 1 patient received rabeprazole 40 mg daily, and 1 patient received omeprazole 20 mg daily. There was no difference in virological outcomes between the 2 groups ($p = 1.00$; 95% CI 0.21–85.97).

Case Reports

Case reports have also yielded conflicting results. In one such report,[15] an HIV-infected patient underwent a 12-h pharmacokinetic study, which supported an interaction between the PPI (esomeprazole) and atazanavir. The 65-year-old patient was receiving an antiretroviral regimen consisting of atazanavir 300 mg with ritonavir 100 mg daily, tenofovir 300 mg daily, and stavudine 30 mg twice daily. The 12-h pharmacokinetic sampling revealed a 90% reduction in C_{min} and a 78% reduction in AUC relative to established therapeutic

ranges of concentrations reported in clinical trials of atazanavir. On the basis of these results, the clinicians caring for the patient increased the dosing regimen to atazanavir 300 mg bid with ritonavir 100 mg bid, but there was no significant improvement in C_{min}. The patient's antiretroviral regimen was subsequently changed; no information on clinical outcome was reported.

An earlier case that minimized the atazanavir–PPI interaction was reported by Kosel and others.[16] A 40-year-old HIV-infected man was receiving lansoprazole 30 mg bid for gastroesophageal reflux disease and Barrett's esophagitis before initiation of antiretroviral therapy. At the time of initiation of the antiretroviral regimen (which consisted of atazanavir 300 mg with ritonavir 100 mg daily, tenofovir 300 mg daily, and lamivudine 300 mg daily), ranitidine was substituted for lansoprazole to avoid the potential interaction between the PPI and atazanavir. Because of therapeutic failure with ranitidine, lansoprazole was restarted 1 month later. The patient's serum atazanavir concentrations were within the target ranges suggested for use of ritonavir-boosted atazanavir with concomitant tenofovir. C_{max} was 4120 ng/mL (target value when atazanavir is used with PPIs and tenofovir = 3443 ± 1412 ng/mL), and C_{min} was 790 ng/mL (target value when used with PPIs and tenofovir = 577 ± 367 ng/mL). No clinical outcomes were reported.

The clinical outcomes associated with atazanavir and concomitant PPI therapy were described in a case report by Chan-Tack and Edozien.[17] Virological suppression was maintained in a 50-year-old HIV-infected African-American man with an atazanavir-based regimen, despite concomitant PPI use. Before starting the atazanavir, the patient had received an antiretroviral regimen containing stavudine, lamivudine, and ritonavir-boosted indinavir for 4 years, followed by 2 years of therapy with a regimen containing stavudine, lamivudine, and nelfinavir; during that time, his viral load remained below 400 copies/mL. Eventually, atazanavir was substituted for nelfinavir because of worsening hyperlipidemia. At the time of the change, the patient's CD4 count was 1095 cells/mm^3 (CD4 percentage = 23%), and the viral load was 88 copies/mL. After 12 weeks, the patient reported 100% adherence but revealed that he was taking omeprazole 20 mg daily for gastroesophageal reflux disease and also that he was taking his atazanavir divided in 2 doses rather than 300 mg once daily as prescribed. At this 12-week follow-up, his CD4 count remained at 830 cells/mm^3 (CD4 percentage = 21%), and viral load was less than 75 copies/mL. Despite the lack of adverse clinical outcome, the patient was switched back to a nelfinavir-containing regimen, along with initiation of statin therapy.

In the final case report identified, the effects on both pharmacokinetic and clinical outcomes were described for a patient receiving atazanavir and PPI therapy.[18] A 56-year-old HIV-infected man with a CD4 count of 494 cells/mm^3 and an HIV RNA load of 64 800 copies/mL initiated a regimen containing atazanavir boosted with ritonavir and tenofovir, along with abacavir and lamivudine. Two months after initiation of this regimen, gastritis developed, which was unresponsive to H2 antagonists; thus, omeprazole 40 mg daily was required. Over the next 10 months, despite concomitant PPI therapy, the patient's viral load remained at or less than 50 copies/mL. An atazanavir trough level, measured in a sample drawn during PPI coadministration about 22 h after an unwitnessed dose of atazanavir, was 0.3 mg/L; this value was below the population-predicted 25th percentile for ritonavir-boosted atazanavir but above the 75th percentile for unboosted atazanavir. As unboosted atazanavir has been shown to achieve rates of viral control similar to those obtained with ritonavir-boosted atazanavir in treatment-naïve patients, the authors considered the measured level adequate.

DISCUSSION

Atazanavir requires a gastric pH below 4 for maximal dissolution and absorption.[4] The manufacturer indicates in the product monograph that PPIs should not be administered with atazanavir and that PPIs may substantially decrease plasma concentrations of atazanavir, resulting in loss of therapeutic effect and development of resistance.[4] Subtherapeutic levels of antiretroviral therapy can yield inadequate suppression of viral replication, increasing the risk of the viral mutation and subsequent drug resistance. Studies involving healthy adults offer proof that a pharmacokinetic drug interaction exists between atazanavir and acid-lowering medications, which potentially puts HIV-infected patients at risk of therapeutic failure. Case reports and retrospective and prospective analyses evaluating the interaction between acid-lowering agents and atazanavir have yielded conflicting results; of note, these studies have typically reported either the effects on pharmacokinetics or the clinical outcome, but seldom both. All of the studies reviewed here are limited by small sample sizes and inability to correlate pharmacokinetic observations with long-term outcomes such as failure of the antiretroviral treatment. In terms of H2 receptor antagonists, Agarwala and others[7] observed that the

pharmacokinetic effects of famotidine on atazanavir could be minimized by temporally separating doses of the 2 drugs or by increasing the dose of atazanavir to 400 mg with ritonavir 100 mg. We found no published articles investigating the possible drug interaction between atazanavir and other antacids or buffered medications. PPIs have a greater impact on the pharmacokinetics of atazanavir than shorter-acting acid-lowering agents, especially if given in higher doses.[6-9] In the abstract presented by Luber and others,[9] omeprazole 20 mg daily added to atazanavir had far less impact than was the case in previous studies using omeprazole 40 mg daily.[6-8]

Several reasons may account for these conflicting results. Experts suggest that plasma concentrations in healthy subjects may not correlate with those of HIV-infected individuals and that HIV-infected patients may be less susceptible to this drug interaction because of a higher prevalence of hypochlorhydria.[14] Another confounding factor is that many of the patients in these studies were receiving tenofovir as part of their antiretroviral regimen, a drug that has been shown to lower atazanavir levels.[19] Atazanavir levels are highly variable and may not always correlate with viral response.[2,9,20] Even though experts suggest maintaining the atazanavir trough concentration above 150 ng/mL, the minimum effective concentration of atazanavir has not been well established, especially in treatment-experienced patients.[21,22]

CONCLUSIONS

Pharmacokinetic studies in healthy volunteers have clearly demonstrated that the bioavailability of atazanavir is compromised when acid-lowering agents are used concomitantly. Although the results of retrospective analyses and case reports are conflicting and do not strongly suggest that concomitant use of PPIs and atazanavir increases the risk of virologic or immunologic failure, long-term studies—especially in treatment-experienced patients—evaluating both pharmacokinetics and clinical response are required to establish the clinical relevance of this interaction. Until then, concomitant use of PPIs and atazanavir should be avoided if possible. If PPI therapy is necessary, the antiretroviral regimen should be changed to an alternative regimen not containing atazanavir, if possible. If the patient is limited to an atazanavir-containing regimen and an acid-lowering agent is required, therapy with an H2 receptor antagonist (with administration temporally spaced from the atazanavir) should be considered first. If PPI therapy is warranted while the patient is receiving atazanavir, the atazanavir should be boosted with ritonavir 100 mg daily and should be given at a minimum of 300 mg daily, the lowest effective dose of PPI should be prescribed, and the patient should be diligently monitored for virologic and immunologic failure. Therapeutic drug monitoring and resistance testing should be performed if treatment failure occurs. Inability to achieve adequate therapeutic levels may warrant an increase in the dose of atazanavir up to 400 mg daily, and evidence of drug resistance may dictate a change in the patient's antiretroviral regimen.

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