Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.elsevier.com/locate/apjtb

Document heading doi:10.1016/S2221-1691(13)60091-X

Acute pancreatitis in HIV/AIDS patients: an issue of concern

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KEYWORDS

Acute pancreatitis
Nucleoside reverse transcriptase inhibitors
Protease inhibitors
CD cells count
Gender

ABSTRACT

Pancreatitis is a well-described complication of human immunodeficiency virus (HIV) itself and its combination antiretroviral therapy. Historically, this has been predominantly associated with the usage of nucleoside reverse transcriptase inhibitors such as didanosine and stavudine, but only rarely with the usage of protease inhibitors via the induction of hypertriglyceridemia. Pancreatitis rates in HIV/AIDS population may have been exceedingly high because of the comorbid conditions prevalent in HIV/AIDS patients (*e.g.* ethanol use and biliary disease), and the use of non-combination antiretroviral therapy medications such as pentamidine, corticosteroids, ketoconazole, sulphonamides, metronidazole, isoniazid and opportunistic infections (*e.g.* cytomegalovirus, cryptosporidiosis, mycobacterial disease). In resource limited settings, where didanosine and stavudine are widely available in cheaper generic fixed dose combinations it is likely that their usage will remain in the first line HIV treatment in common. In such settings management or estimation of a patient's risk of pancreatitis still remains an issue of concern.

1. Introduction

Acute pancreatitis is potentially life-threatening condition that is characterised clinically by abdominal pain, nausea, vomiting, and biochemically by elevations of lipase and/or amylase. Although the annual incidence in the general population is relatively low, estimated to be 17 to 30 cases per 100 000 population[1], the annual incidence of acute pancreatitis in the patients with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) is considerably higher[2].

Pancreatitis is a well-described complication of HIV itself and its combination antiretroviral therapy (cART)[2-4]. Historically, this has been predominantly associated with the usage of nucleoside reverse transcriptase inhibitors (NRTIs) such as didanosine and stavudine[5-7], but only rarely with the usage of protease inhibitors (PIs) via the induction of hypertriglyceridemia[8,9]. Therefore, pancreatitis rate in HIV/AIDS population may have been exceedingly high because of the comorbid conditions prevalent in HIV/AIDS patients (*e.g.* ethanol use and biliary disease), the use of non-cART medications such as pentamidine, corticosteroids, ketoconazole, sulphonamides, metronidazole, isoniazid and opportunistic infections (*e.g.* cytomegalovirus, cryptosporidiosis, mycobacterial disease)[10-12]. In the pre-highly active antiretroviral therapy (HAART) era, the reported incidence among HIV-infected patients has been wide-ranging. One study found an incidence of 6.7 cases per 1 000 person-years (PYs) in their cohort of 939 patients followed for seven years[6]. Dutta *et al.* demonstrated a much higher incidence, 140 cases per 1 000 PYs, in a group of 321 patients followed for one year[3]. Dassopoulos *et al.* found an incidence of clinical acute pancreatitis of 6.1 per 1000 PYs, as well as a much higher rate of laboratory evidence of pancreatic abnormalities (22.3 per 1 000 PYs)[4]. Chehter *et al.* discovered frequent pancreatic involvement (90%) in a post-mortem study of AIDS-related deaths, although the majority of these patients did not have clinically apparent pancreatic disease before death[13].

The aim of this review article is to offer the current summary of the most frequently present risk factors for acute pancreatitis, such as NIRTs, PIs, CD4 cell count or gender in HIV/AIDS patients receiving highly active antiretroviral therapy.

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Foundation Project: The work was part of the project of the FP 6 program (Grant No.: 175024) supported by Ministry of Science and Technological Development of Serbia together with "European AIDS Treatment Network" (NEAT): LSHPCT-2006-037570.

Article history:
Received 12 Apr 2013
Received in revised form 20 Apr, 2nd revised form 29 Apr, 3rd revised form 1 May 2013
Accepted 26 May 2013
Available online 28 June 2013

2. The most common risk factors for acute pancreatitis in HIV/AIDS patients

2.1. NRTIs and pancreatitis

Reisler *et al.* found that the single or dual combination of NRTIs selected to be a part of cART seem to have an impact on the incidence of pancreatitis. Of the various combination of single and dual NRTIs that they studied, didanosine, stavudine and their combination (didanosine+stavudine) seem to be associated with particularly high rates of pancreatitis, reminiscent of high-dose didanosine monotherapy trials. In the multivariate logistic regression model, Reisler *et al.* found that of all nucleoside combinations included in the analysis, the combination of didanosine/stavudine was associated with the highest rates of pancreatitis[14].

The frequency of didanosine-induced pancreatitis seems to be dose related[15]. The high didanosine plasma levels may be associated with higher rates of pancreatitis when the daily dosage of didanosine was 400 mg, combind with 300 mg of tenofovir[15]. Coadministration of tenofovir with didanosine increases the maximum plasma concentration and area under the curve of didanosine by 48% to 64%[15,16]. Therefore, the risk of acute pancreatitis is heightened when didanosine and tenofovir are given together. In 2004, Martinez *et al.* shown that didanosine, even at a dose of 250 mg daily, when given with tenofovir is associated with increased risk of pancreatitis, especially in women weighing 60 kg or less[16]. A further risk factor for pancreatitis among HIV-positive individuals previously observed is the use of hydroxyurea, particularly in combination with didanosine, which is no longer used in Europe and the USA[17].

Riedel *et al.* shown that of 5970 patients followed for 23460 PYs, there were 85 episodes of acute pancreatitis (incidence: 3.6 events/1000 PYs). They concluded in their multivariate logistic regression analysis that the factor associated with pancreatitis was stavudine usage (*OR* 2.19; 95% *CI*=1.16, 4.15; *P*=0.016)[18]. Several other studies have shown that the administration of stavudine 40 mg/d can be associated with acute pancreatitis[19-21]. These studies of stavudine toxicity are all limited by the fact that patients over 60 kg were exposed to a dosage of 40 mg/d. In 2007 WHO has recommended dosing 30 mg of stavudine daily, irrespective of weight, as this is equally effective with a potentially lower rate of side effects[22]. In accordance with this, recently published studies by Maskew *et al.* and by Pujades-Rodríguez *et al.*, have shown that reduced dose of stavudine from 40 to 30 mg/d, can minimize the incidence of all side effects, including acute pancreatitis[23,24].

Colette Smith and the Euro SIDA collaborators, concluded that there is no evidence of an association of pancreatitis with cumulative exposure to didanosine and stavudine, didanosine without stavudine, stavudine without didanosine, or any other ART. They found no evidence that cumulative exposure to any other antiretroviral regimens was associated with an increased risk of pancreatitis. Every relative risk influencing acute pancreatitis appearance they estimated, were close to one, suggesting that any effect of antiretroviral therapy on the occurrence of pancreatitis is likely to be small. However, they also observed a low incidence of pancreatitis within the EuroSIDA study, and there was no evidence to suggest an increase over time in the years 2001-2006[25].

The specific mechanism of NRTI-induced pancreatitis is not yet known[26]. Mitochondrial toxicity is the common pathway of several NRTI adverse effects[11,26,27]. Given the similarities in function between HIV reverse transcriptase and human DNA polymerases, it is not surprising that nucleoside analogues are competitive inhibitors of human DNA polymerases-gamma, a key enzyme for mitochondrial DNA replication. The accumulation of mitochondrial DNA deficits induces a deficient production of molecules devoted to the intramitochondrial synthesis of adenosine triphosphate. Once adenosine triphosphate production drops below a certain threshold, sudden mitochondrial and then cellular damage occurs that can lead to cell death. Tissues and organs cannot function properly, and the damage becomes clinically apparent[26]. The clinical use of NRTI has been associated with adverse effects caused by mitochondrial dysfunction, such as acute pancreatitis, myopathy, peripheral neuropathy, anemia, neutropenia, hepatic toxicity and hyperlactataemia/lactic acidosis[28-30].

2.2. PIs and pancreatitis

In the pre PI-based HAART, and after the introduction of PIs, the most common cause of pancreatitis in HIV-infected patients was medication-induced pancreatitis[7,17,21]. PI therapy, introduced in 1996 for HIV infection, is associated with moderate to severe hypertriglyceridemia[8,31]. Hypertriglyceridemia is a well-established cause of acute pancreatitis in the general population. Despite of the well-established association between PIs and hypertriglyceridemia, there was no significant increase in the prevalence of hyperlipidemic pancreatitis in this HIV-infected population after the introduction of PIs[32].

PI-based HAART regimens were not associated with an increased risk of pancreatitis. The severe metabolic changes in AIDS patients may play a role in ultrastructural histologic changes found in the pancreas[12]. The hypertriglyceridemia associated with PI use is often severe and difficult to treat, and it may reasonably be expected to lead to an increased risk of hyperlipidemic pancreatitis in the HIV-infected population[8,9].

In 2007, Chapman *et al.* reported one of the first cases of severe hypertriglyceridemia associated with the administration of tipranavir-ritonavir leading to acute pancreatitis[33]. Tipranavir, a non-peptidic HIV-1 PI, co-administered with 200 mg of ritonavir, was granted accelerated US FDA approval for combination antiretroviral treatment of HIV-1 infected adult patients. This case illustrates that tipranavir can be associated with the rapid development of extreme triglyceride levels, which can be associated with patient morbidity[33].

In addition to the close monitoring of patients for hepatic enzyme abnormalities, this group of authors suggested that close monitoring of serum lipid concentrations in patients taking tipranavir is warranted, especially in those with a history of raised serum triglyceride levels[33,34]. Conversely, should a patient present with pancreatitis while on tipranavir-containing regime, physicians should be mindful of the possibility of hypertriglyceridemia-induced pancreatitis[35].

2.3. CD4 cell count and pancreatitis

The risk of pancreatitis is increased for the HIV/AIDS patients with lower CD4 cell counts[36]. There is also evidence of an association with higher viral loads, suggesting that those with more advanced disease are at greater risk[17,21,35].

In order to support this statement, Riedel conducted a clinical trial and concluded that the HIV/AIDS patients with severe immunosuppression (*i.e.*, CD4<50 cells/mm^3), (*OR* 10.47; 95% *CI*=3.33-32.90; *P*<0.001) are in the higher risk to develop acute pancreatitis[18]. There are multiple potential causes for this association: at low CD4 counts (*i.e.*, <200 cells/mm^3), HIV patients are prone to opportunistic infections, of which many have been associated with pancreatic involvement[10]. Medications for opportunistic infections prevention and treatment, including pentamidine and trimethoprim-sufamethoxazole, have also been associated with pancreatitis. Metronidazole itself could also induce acute pancreatitis[37-39]. Lastly, CD4 lymphocytes could be important in preventing the acinar cell necrosis which leads to clinical acute pancreatitis[3].

Consistent with prior studies, Dragovic *et al.* also demonstrated an increased risk of pancreatitis with worsening immunosuppression, particularly at the lowest CD4 counts, even after adjustment for HAART use[21].

2.4. Gender and pancreatitis

The female sex has been implicated as a risk factor for pancreatitis in HIV/AIDS patients. Riedel *et al.* concluded that there is an association between female gender and acute pancreatitis[18]. In contrast with this, Euro SIDA group found there is no sex difference in and no association between pancreatitis and body mass index[25]. The reasons to observe sex differences in toxicity rates are uncertain. Differences in BMI, fat composition, hormonal status, drug disposition and metabolism may play a role individually or in concept[40]. This may suggest an increased sensitivity of women to the toxicity of the NRTI containing regimens may be due to a smaller body mass index[40,41].

3. Conclusion

In the era of potent antiretroviral therapy, pancreatitis in HIV-infected patients is still most commonly due to drugs, including antiretroviral agents and medications used to treat or prevent opportunistic infections. Since the introduction of PIs, alcohol also remains an important cause of pancreatitis in HIV-infected patients, whereas gallstones rarely cause pancreatitis in this population.

Standardization of pancreatitis definition and more comprehensive evaluations are needed to determine how much of pancreatitis is directly caused by ARVs and how much is attributable to pre-existing comorbidities and other known factors. Therefore, rates of acute pancreatitis are lower in Western Europe, US and Canada in comparison with those in resource limited settings where the new and less toxic antiretroviral drugs are still not available. In resource limited settings didanosine and stavudine are widely available in cheaper generic fixed dose combinations. Therefore, it is likely that didanosine and stavudine use will remain common in the first line HIV treatment in countries where access to alternative regimens is limited by cost. In such settings, management or estimation of a patient's risk of pancreatitis still remains an issue of concern.

Conflict of interest statement

I declare that I have no conflict of interest.

Acknowledgements

The work was part of the project of the FP 6 program (Grant No.: 175024) supported by Ministry of Science and Technological Development of Serbia together with "European AIDS Treatment Network" (NEAT): LSHPCT - 2006-037570.

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