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Myalgia and creatine phosphokinase elevations in the HAART era: focus on Raltegravir

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ABSTRACT

Raltegravir is the first HIV integrase inhibitor available in clinical practice for the treatment of HIV-infection in both naive and experienced patients. Randomized clinical trials have evidenced a good safety profile. However, grade III-IV creatine phosphokinase increases have been more frequently observed in patients receiving raltegravir in respect of comparator treatments and cases of rhabdomyolysis has been reported in the literature. In this article, we give an insight into the available data from clinical studies and case reports and possible pathogenetic mechanisms of raltegravir-related muscle toxicity.

Introduction

The introduction of Highly Active Antiretroviral Therapy (HAART) for the treatment of HIV infection has led to a improved survival and better quality of life in a large number of subject that can be managed as chronic patients [1-3]. However, in a growing number of subjects multiple drug resistance to the historical antiretroviral drug classes protease inhibitors, nucleoside reverse transcriptase inhibitors and non nucleoside reverse transcriptase inhibitors have been selected over time. The introduction of new drugs in "old" classes (darunavir, tipranavir) and of new drug classes (fusion inhibitors, integrase inhibitors and CCR5 antagonists) have deeply changed the scenario for the multi-experienced patients that can be now considered as "new naives" after more than a decade of HAART receipt. All HIV therapy guidelines agree in identifying at least two fully active potent drugs included in the regimen to obtain maximal viral suppression and immune reconstitution.
Raltegravir is the first HIV integrase inhibitor available in clinical practice for the treatment of HIV-infection in both naive and experienced patients [4-7]. Raltegravir inhibits the strand-transfer step of integration by blocking the enzyme's active site. With raltegravir present, the preintegration complex is unable to bind to host DNA [8, 9]. The nonintegrated proviral HIV DNA is repaired via normal cellular DNA repair mechanisms and is rendered inactive [10]. In contrast to most other antiretroviral drugs, raltegravir is metabolized by glucuronidation via UGT1A1 [11, 12]. Excretion in feces (51%) and in urine (31%) accounts for most of the elimination. No dose adjustment is required for gender, age, hepatic or renal function, or body mass index [13].
Randomized clinical trials have evidenced a good safety profile. However, some cases of muscle toxicity emerged from clinical studies and case reports.

Definition of myopathies

Skeletal muscle involvement may occur at all stages of HIV infection and may be classified as follows: HIV-associated myopathies; muscle complications of antiretroviral therapy; opportunistic infections and tumor infiltrations of skeletal muscle and rhabdomyolysis.
In the literature, the terminology used to describe muscle drug toxicity is not generally standardized. Therefore, the ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins produced a document in 2002 to help standardize the definitions related to muscle damage [14]. Myopathy was defined as a general term referring to any disease of muscles; Myalgia as muscle ache or weakness without creatine phosphokinase (CKP) elevation; Myositis as muscle symptoms with increased CPK levels and Rhabdomyolysis as muscle symptoms with marked CK elevation (typically substantially greater than 10 times the upper limit of normal [ULN]) and with creatinine elevation (usually with brown urine and urinary myoglobin) [14].

The role of antiretroviral therapy

Among antiretroviral drugs the most studied in the pre-HAART era was zidovudine. Zidovudine myopathy is a reversible toxic mitochondrial myopathy occurring in patients who have received high cumulative doses of the drug. Clinically, it mimics HIV-associated polymyosistis. Histologically, it is characterized by the presence of "AZT fibers," a term coined by Dalakas to designate atrophic ragged-red fibers with marked myofibrillar alterations, including thick myofilament loss and cytoplasmic- body formation [15, 16].

Although the impact of HAART on the prevalence of muscle involvement was not established by epidemiological studies, such an impact seems quite likely in practice, as suggested by the marked decrease of muscle biopsies performed in HIV-infected individuals [17].

As mentioned before raltegravir has proved highly effective in both naive and experienced patients in clinical trials [4-7].

When analyzing the phase II and III trials together, only a few patients on raltegravir or placebo discontinued because of adverse events that were mostly mild to moderate. Regarding toxicity, study 005 and BENCHMRK trials are more difficult to interpret because patients received complex antiretroviral regimens. Study 004 and the STARTMRK study are more informative with regard to muscle toxicity considering that all patients received the same backbone of tenofovir/lamivudine or tenofovir/emtricitabine, respectively.

In study 004 after 96 weeks follow up patients receiving raltegravir had a higher frequency of grade III-IV CPK increases in respect of efavirenz treated patients (6.3% vs 2.6%) but this laboratory abnormality did not lead to discontinuation or clinical events of myopathy and rabdomyolisis. The extended follow up showed a with a slight increase at week 144 (8.8% vs 2.6%) and a stability at week 192 (8.8% vs 5.3%), as illustrated in Table 1 [5, 18].

In the BENCHMRK 1-2 studies the proportion of patients experiencing CPK increase >10 ULN (grade III-IV) was 6.9% in raltegravir treated in respect of 3.3% in placebo plus OBT harm. CPK elevations were not associated with clinical myopathy, myositis, or rhabdomyolysis and did not lead to treatment interruption or discontinuation, in these patients (Table 1)[6].

Furthermore, in the SWITCHMRK studies no significant muscle toxicity was reported or led to discontinuation [19].

Although most safety data regarding muscle adverse events are available only from clinical trials, some case reports have been published in the literature since the introduction of raltegravir.

Four cases of rhabdomyolysis have been reported in patients receiving raltegravir to date (Table 2) [20-23]. In these cases risk factors for rabdomyolysis were present in different associations. Interestingly, the time to event onset was very variable and ranged from 10 days to 23 months. The most rapid event was reported by Croce et al. in a 47 years old female who started raltegravir with abnormal CPK levels after an asymptomatic CPK increase related to her previous antiretroviral regimen that included zidovudine and tenofovir/emtricitabine [23].

In the first published case, the patients was a 46 years old African- American who was receiving a very complex antiretroviral regimen and concomitant therapy for opportunistic infections includ-

Table 1. Muscle toxicity in raltegravir clinical trials.

Protocol	Study design	Population	Treatment arms	Muscle adverse events
004 [5]	Multicenter, double-blind, randomized, controlled, dose-escalating	antiretroviral naive (n = 198)	RAL 100, 200, 400, or 600 mg bid vs EFV 600 mg qd (all + 3TC and TDF)	Grade III-IV CPK elevations: Week 96: 6.3% in RAL vs 2.6% in EFV Week 144: 8.8% in RAL vs 2.6% in EFV Week 192: 8.3% in RAL vs 5.3% in EFV No cases of myopathy, myositis, or rhabdomyolysis and no therapy discontinuation caused by muscle toxicity
005 [7]	Multicenter, double-blind, randomized, controlled, dose-escalating	treatment-experienced, multidrug-resistant (n = 178)	RAL 200, 400, and 600 mg bid vs placebo (+ optimized background regimen in all)	Not reported
BENCHMRK 1-2 (018-019) [6]	Phase III, parallel, multinational, randomized, double-blind, placebo-controlled studies	treatment-experienced, multidrug-resistant (n = 350; n = 349)	RAL 400 mg bid vs placebo (+ optimized background regimen in all)	Grade III-IV CPK elevations: Week 96: 6.9% in RAL vs 3.3% placebo + OBT
STARTMRK (021) [4]	Phase III multinational, double-blind, randomised trial.	antiretroviral naive (n = 566)	RAL 400 mg bid vs EFV 600 mg qd (all + FTC and TDF)	Not reported

RAL: raltegravir; EFV:efavirenz; 3TC lamivudine; TDF: tenofovir; FTC: emtricitabine.

ing clarithromycin and itraconazole which have been shown to cause rhabdomyolysis [20]. CPK values were normal before starting raltegravir. Surprisingly clinically overt rhabdomyolysis with muscle pain and weakness developed 2 weeks after raltegravir discontinuation and CPK values did not return within normal range whereas symptoms resolved in four days after aggressive hydration. Therefore, the causal relation with raltegravir, as the authors admit, is difficult to determine [20].

In the remaining 3 cases, the causal relation with raltegravir appears stronger but some other identifiable risk factors were present [21-23]. In all cases patients were receiving tenofovir that has been, even if rarely, associated with rabdomyolisis and that can increase raltegravir concentrations. In one case the patient was receiving pravastatin that was previously well tolerated. In 2/4 cases rhabdomyolysis developed with a concomitant intense physical effort.

The pathogenetic mechanism underling raltegravir-related muscle toxicity is not known. However, some mechanism could be hypothesized.

Most of the studies regarding the pathogenesis of drug-related myopathies involve statins and range from asymptomatic iperCKemia or benign myalgia to rarely fatal necrotizing rhabdomyolysis. In some patients statins may initiate immune-mediated necrotizing inflammatory myopathy or aggravate or unmask a metabolic myopathy or other neuromuscular disorder.

It is well known that the risk of statin myopathy is increased by co-administration of other drugs that are inhibitors of cytochrome P450 (CYP)3A4, which metabolizes simvastatin, atorvastatin and lovastatin [24]. A recent review at the FDA Centre for Drug Evaluation and Research compared the risk of rhabdomyolysis associated with simvastatin and pravastatin over the period 1991–2001 by concomitant administration of a CYP3A4 inhibitor and confirmed that there was an increased risk for simvastatin but not for pravastatin [25]. Of the simvastatin-associated cases taking a single CYP3A4 inhibitor he most frequent co-medications were clarithromycin, mibefradil, verapamil, nefazodone, cyclosporine, diltiazem and itraconazole [25].

In consideration of the previous experience with statins, the use of raltegravir should be considered with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions [12].

Gene expression studies have shown that high-dose statins have multiple effects on metabolic and signalling pathways related to carbohydrate oxidation, transmembrane transport, proteasomal and lyso-

Table 2. Case reports of rhabdomyolysis in patients receiving raltegravir.

	Patient 1 [20]	Patient 2 [21]	Patient 3 [22]	Patient 4 [23]
Race	African-American	Caucasian	n.a	Caucasian
Age (years)	46	69	44	47
Gender	Male	Male	Male	Female
CD4 cell nadir	17	174	n.a.	322
HAART regimen	Enfuvirtide, darunavir, ritonavir, etravirine, raltegravir	Lopinavir/r, tenofovir/ emtricitabine, raltegravir	Tenofovir/emtricitabine, raltegravir	Tenofovir/emtricitabine, raltegravir
Concomitant medications	Clarithromycin, ethambutol, rifabutin, itraconazole, trimthoprim-sulfametoxazole, valaciclovir, foscarnet, filgrastim	Sertraline, pravastatin	NSAIDs	Citalopram, vitamin K, rifaximin
Co-morbidithies	Chronic renal failure	Hypercholesterolemia	HCV infection	Hepatic cirrhosis (HCV-related), hypetrygliceridemia, hyperglycemia, lipodystrophy, major depression
Time to event	7 months	2 months	23 months	10 days
Previous drug-related CPK increase	no	no	no	Yes
Abnormal CPK at baseline	no	no	no	Yes
Concomitant physical effort	no	yes	no	Yes

NSAIDs: nonsteroidal anti-inflammatory drugs; CPK: creatine phosphokinase; n.a.: not applicable.

somal proteolysis, apoptosis and pro-inflammatory pathways [26-28]. There is increasing evidence that genetic factors are important in determining the risk of developing a statin myopathy, as outlined in the recent review by Ghatak et al. [29].
Raltegravir is metabolized by glucuronidation in the liver via UDP-glucuronosyltransferase 1A1 (UGT1A1). The effect of hepatic impairment on the drug pharmacokinetics and the clinically meaningful significance of UGT1A1_28/_28 polymorphisms, associated with reduced UGT1A1 activity and subsequent increases of plasma RAL concentrations, are still not clear. Furthermore, it should be considered that in the case reported by Croce et al the patients was negative for UGT1A1_28/_28 polymorphisms [23].
Of practical importance also in HIV-infected patients could be recent reports of reduced vitamin D levels in the serum of patients with statin associated myalgia with resolution of myalgic symptoms after vitamin D repletion, suggesting that there may be a reversible interaction between vitamin D deficiency and the effects of statins [30, 31]. The prevalence of vitamin D deficiency in the Italian HIV population has been recently evaluated in the ICONA cohort in 54% of patients and seems related with older age, lower BMI, lower CD4 cell count and Caucasian origin [32]. These data suggest that vitamin D levels should be evaluated in all patients and probably could play a role in different HIV-related co-morbidities and possibly myopathies.
To date the only data from clinical practice observational cohorts derive from the Italian SCOLTA Project. In a recent oral presentation at the Tenth International Congress on Drug Therapy in HIV Infection preliminary results on 291 raltegravir-treated patients were presented [33]. A significantly higher frequency of muscle symptoms (especially muscle weakness) in patients receiving raltegravir was evidenced in respect of a control cohort of patients receiving darunavir. In the same evaluation, CPK elevations in patients with normal baseline values occurred in almost 10% of patients without significant differences between groups suggesting a multifactorial aetiology in HIV patients receiving HAART. Interestingly, no relation emerged between CPK increases and muscle symptoms and no therapy discontinuation was observed. These results suggest that most cases are of mild clinical entity even in a non selected clinical casuistry. Further analysis and a longer follow up could better identify specific risk factors for muscle toxicity in HIV patients that should be considered before starting raltegravir.

Conclusions

Raltegravir is a safe and very effective antiretroviral drug which has proved useful in the management of HIV infective patients in different clinical scenarios including experienced patients with limited treatment options, naïve patients and patients with stable infection for switch strategies, when correctly selected.
HIV-infected patients should be screened for ongoing CPK increase and raltegravir should be initiated only in those with normal levels. Patients with asymptomatic CPK increase and/or with known risk factors for rhabdomyolysis should be closely monitored if raltegravir is started. Moreover, patients receiving raltegravir should be routinely monitored for the onset of muscle symptoms, independently of CPK levels and risk factor such as concomitant medications and physical activity should be revised at each clinical evaluation.
Further studies are needed to better clarify the prevalence, pathogenetic mechanism, specific risk factors and management of muscle toxicity in raltegravir-treated HIV patients.

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