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Short communication

Dolutegravir monotherapy as treatment de-escalation in HIV-infected adults with virological control: DoluMono cohort results

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Abstract

Background: The potential toxicity of long-term antiretroviral treatment (ART) requires ongoing investigation of novel strategies for treatment of HIV-infected patients. Monotherapy with the integrase inhibitor (INSTI) dolutegravir (DTG) may offer a favorable safety profile. Additionally, DTG has a high barrier of resistance, crucial for successful maintenance of virologic control. However, published data is sparse.

Methods: Retrospective, single-center cohort study. We enrolled patients on suppressive ART who were switched to DTG monotherapy in routine clinical practice and fulfilled the following inclusion criteria: HIV RNA level <50 copies/mL for ≥6 months at time of switch (one blip <200 copies/mL with re-suppression accepted), no known INSTI resistance or prior INSTI failure, no replicative hepatitis B virus infection, and no history of AIDS.

Results: We identified 31 patients with 24-weeks of follow-up data. Previous ART included an NNRTI, a boosted PI, or an INSTI in 32%, 6% and 61% of patients, respectively. At week 24, HIV RNA remained <50 copies/mL in all but two patients (94%). One patient chose to discontinue DTG monotherapy, and another developed confirmed virologic failure (HIV RNA 538 copies/mL) with new INSTI mutations (Q148H/G140S). Immune status and renal and metabolic function showed no statistically significant changes, apart from a significant decrease in GGT.

Conclusions: De-escalating to DTG monotherapy in selected patients might be safe and feasible option. However, in one case evolution of INSTI resistance was observed. Further studies should assess particular risk factors for DTG monotherapy failure. In the meanwhile, caution is warranted.

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Running head: DTG monotherapy de-escalation in suppressed HIV-infected adults

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Introduction

Modern combination antiretroviral therapy (ART) leads to control of HIV infection and allows a potentially normal life expectancy [1]. Nucleoside reverse transcriptase inhibitors (NRTIs) play a major role as the “backbone” of ART, and are considered essential in current HIV treatment guidelines [2]. However, NRTI use is associated with significant side effects [3–5], particularly after long-term exposure [6]. Hence, alternative NRTI-free therapy options have been evaluated in different studies, but are associated with lower rates of virologic success and higher rates of therapy-induced resistance compared to standard regimens [7,8]. Monotherapy with boosted protease inhibitors (bPI) offers a high genetic barrier of resistance [9] and ritonavir-boosted darunavir (DRV/r), with its once-daily dosing option and well-established safety profile, has shown the highest efficacy in terms of virologic suppression [9–11]. However, bPI monotherapy has been shown to be more efficient in achieving continued HIV RNA suppression in patients with a fully suppressed viral load (HIV RNA <50 copies/mL) at inclusion, a known CD4-nadir >200 cells × 10^9, and no known previous non-NRTI use [10,11]. In the majority of patients with observed virologic failure on bPI monotherapy, re-intensification of ART, i.e., switching to standard of care therapy (SOC), decreased HIV RNA to <50 copies/mL. Therefore, bPI monotherapy is suggested as an option for a defined HIV-infected population [12], but is still associated with an unfavorable metabolic profile, tolerability concerns, and food restrictions.

The novel second-line HIV integrase inhibitor (INSTI) dolutegravir (DTG) is highly effective for treating HIV-infection in combination with other antiretroviral agents in phase III trials and as a single agent in phase IIa trials [13]. In this context, DTG’s high level barrier of resistance might be comparable to that of bPIs [14]. Data on DTG monotherapy is sparse [15–17]. However, evidence has highlighted the necessity of diligent patient selection for DTG monotherapy strategies, to prevent emergence of HIV INSTI resistance [17,18].

Our study aimed to investigate DTG monotherapy as de-escalation therapy in routine clinical practice in a select population of previously well-treated and fully suppressed HIV-infected patients.

Design

Retrospective analysis of a single-center cohort study.

Methods

The study was performed in a large specialized HIV clinic in Munich, Germany. Patients switched to DTG monotherapy based on the clinical judgment of the treating physician were screened for inclusion. Ethics committee of Technische Universität München (TUM), Munich, Germany approval (No. 359/15) for retrospective evaluation was obtained and all participants provided written informed consent. Inclusion criteria were: HIV RNA <50 copies/mL for at least 6 months prior to study inclusion

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(one blip <200 copies/mL with subsequent re-suppression to <50 copies/mL was accepted); no documented HIV INSTI resistance or prior INSTI failure; absence of replicative hepatitis B virus infection; no history of AIDS; and no contraindication to DTG, based on laboratory safety parameters. All patients with follow-up data at week 24 were included in the primary analysis.

All parameters, as available within routine clinical practice, were extracted from patients' records between August 2015 and May 2016. At week 24, HIV RNA was extracted for primary descriptive efficacy analysis. CD4(absolute), CD4%(relative), CD8(absolute), and CD4/CD8-ratio, and changes in CD4, CD8, and CD4/CD8-ratio; safety and tolerability (adverse events); reported adherence and information about virologic failure; changes in renal function (serum creatinine, creatinine-based (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)) estimated glomerular filtration rate [eGFR]); changes in liver function (alanine transaminase [ALT], aspartate transaminase [AST], gamma-glutamyl transferase [GGT], total bilirubin); changes in metabolic profile (triglycerides and high-density lipoprotein [HDL]-, low-density lipoprotein [LDL]- and total cholesterol) within the 24-week study period, were documented.

Statistical analysis was performed using Stata Statistical Software (Release 13. College Station, TX: StataCorp LP). Unless stated otherwise, results presented are medians (and inter-quartile ranges). For variable frequencies changing during the course of the study, the McNemar-Test was used. For comparison of continuous variables within groups (paired observations) the Wilcoxon-signed-rank-test was used; α-levels <0.05 were considered as statistically significant.

Results

Of the 31 patients who had follow-up data until week 24, the majority (94%) were of non-black ethnicity, and 68% were male. Median age was 44.5 (34.9–53.9) years. Risk of HIV infection was documented as follows: 18 (58%) men having sex with men (MSM), 8 (26%) heterosexual, 3 (10%) originated from high prevalence countries, 1 (3%) vertical transmission, and 1 (3%) unknown. One patient was co-infected with hepatitis C virus.

Previous antiretroviral combination regimens contained an NNRTI, a bPI or an INSTI in 32%, 6% and 61% of patients, respectively. The INSTIs used were elvitegravir (EVG) in 1 patient, raltegravir (RAL) in 1 patient, and DTG in 17 patients. HIV RNA at baseline was not detectable in 19 (61%) patients, <20 copies/mL in 10 (32%) patients, and 21–49 copies/mL in 2 (6%) patients (COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0). Reasons for switching included gastrointestinal toxicity (n=10), renal toxicity (n=11), drug-drug-interactions on prior ART (n=3), simplifying of ART (n=3), bone toxicity (n=2), lipodystrophy (n=1) and anemia potentially associated to previous ART (n=1). One patient chose to discontinue DTG monotherapy after 19 weeks of treatment, in the absence of drug-related adverse events, while HIV RNA was documented to be undetectable. He attributed an ongoing cough to the use of DTG, although this was unrelated to DTG in the opinion of the treating physician.

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At week 24, HIV RNA was not detectable in 16 (52%) patients, <20 copies/mL in 10 (32%), 21–49 copies/mL in 3 (10%), and 538 copies/mL in one (3%) patient; there was one discontinuation prior to week 24 (classified as failure in ITT (intention-too-treat) snapshot analysis). Overall virological efficacy at week 24 was 94% (29/31), detailed individual HIV RNA kinetics are displayed in table 1. No significant changes in CD4-cell count and renal or metabolic parameters were found. GGT decreased significantly from baseline to week 24 (median 36 (28–64) U/L vs. 30 (23–51) U/L, respectively, p=0.014).

The patient with confirmed virological failure at week 24 had known HIV infection for 13 years prior to study enrolment. Prior to the switch, his HIV RNA was suppressed (<20 copies/mL), CD4-cell count 1,024 × 10^9 (41%) with a CD4/CD8 ratio of 1.3. ART was initiated with emtricitabine/tenofovir disoproxil fumarate (F/TDF) + efavirenz (EFV) and was switched to F/TDF in combination with DTG 5 years and 11 months prior to DTG switch. HIV RNA was < 50 cps/ml at any single time point with no documented virological failure in patient's history. Arterial hypertension, hypercholesterolemia, erectile dysfunction, and non-alcoholic fatty-liver disease were documented as co-morbidities. Co-medication consisted of cholecalciferol, atorvastatin, amlodipine, valsartan, and sildenafil. HIV RNA remained suppressed (<20 copies/mL) until week 12 (CD4-cell count 1,131 × 10^9, 40%). At week 24, the patient had detectable HIV RNA (538 copies/mL). Despite immediate adherence consulting, virological failure was confirmed with delay due to change of treating out-patients' clinic 5 weeks later: the HIV RNA had increased to 11,000 copies/mL, and the CD4-cell count was 1,008 × 10^9 (38%) with a CD4/CD8-ratio of 1.2. Genotypic HIV resistance analysis revealed no NRTI- or NNRTI-related mutations, A71V as a minor PI-related mutation, and Q148H and G140S as INSTI-related mutations. ART was immediately changed to F/TDF plus ritonavir-boosted darunavir once daily. After 12 weeks on this regimen, the HIV RNA decreased to 190 copies/mL again.

Discussion

Prevention of drug toxicity and ART simplification strategies play crucial roles in maintaining the life-long therapy of HIV-infected patients. Novel treatment strategies might therefore include one- or two-drug-regimens besides the well-established combination therapy, as novel antiretroviral agents offer higher antiviral potency; more tolerable side effect profiles; and simple, once-daily administration. Whereas monotherapy strategies might not be favorable in general populations, they may be an option for carefully selected patients.

We found a safe and effective use of DTG monotherapy as a de-escalation treatment strategy in selected patients on fully suppressive ART, without AIDS. DTG monotherapy was well tolerated; no drug related adverse event was documented. No significant changes in renal- or metabolic-function were found. GGT decreased significantly, although only 3 patients had been switched from nevirapine-containing ART.

DTG monotherapy demonstrated high efficacy with 94% of patients sustaining virologic suppression at week 24, but we observed one case of confirmed virologic failure. In this case, there

was no available information concerning prior INSTI resistance mutations. The patient was diagnosed as HIV-infected prior to the availability of INSTIs and he had no history of INSTI exposure. Therefore, we assume that the INSTI-related mutations Q148H and G140S emerged while on DTG monotherapy. As INSTI mutations may play a key role in future ART of patients—who need life-long treatment—their evolution should be avoided, whenever possible. In line with other studies observing virologic failure after in DTG monotherapy [15,16,18,19], this leads to the hypothesis that only selected patients might qualify. We aimed to prevent patients from DTG monotherapy failure. Patient selection (to switch) was based on prior bPI monotherapy study data, with the absence of low nadir CD4-count, absence of an AIDS events, and stable ART within the last 24 months prior to switch being used as protocol-defined inclusion and exclusion criteria. However, no specific risk factors have been identified as potential predictors of DTG monotherapy failure, as yet and should be addressed in further prospective studies.

To conclude, de-escalation to DTG-monotherapy was a feasible treatment option in the majority of these well-selected patients. However, further prospective trials need to address safety and in particular efficacy of DTG monotherapy strategy. Meanwhile, careful use of INSTI monotherapy, with close treatment monitoring, is essential to prevent the emergence of INSTI resistance with potential loss of an important class of ART, when no other treatment options are available.

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Conflicts of interests

COL has received grants for travel and participation in advisory boards or speaker's honoraria from AbbVie, Bristol-Meyers Squibb, Gilead, Janssen-Cilag, MSD Sharp and Dohme, and ViiV Healthcare.

CDS has received grants for travel and participation in advisory boards or speaker's honoraria from AbbVie, Astellas, Bristol-Meyers Squibb, Gilead, Janssen-Cilag, MSD Sharp and Dohme, and ViiV Healthcare. C.S. has also received grants for investigator-sponsored studies from Gilead Sciences, Janssen-Cilag, and ViiV Healthcare.

EWO has received research lecture sponsorships or has served as a consultant or speaker on advisory boards for AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Hexal, Janssen, Sharp and Dohme, Roche, and ViiV Healthcare.

All other authors declared no competing conflicts of interests.

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Table 1. Overview of all available HIV RNA data from all subjects

Subject No.	Baseline	Week 4	Week 12	Week 24
1	<20		TND	<20
2	<20		<20	TND
3	TND	<20	TND	TND
4	TND		<20	TND
5	TND	TND	<20	<20
6	<20	TND	<20	<20
7	TND	TND		<20
8	TND	TND		TND
9	TND	TND	TND	TND
10	TND	TND	TND	<20
11	36	<20	TND	<20
12	TND	<20	TND	TND
13	<20			36
14	<20	TND	TND	<20
15	TND	TND	TND	TND
16	TND	TND	TND	TND
17	<20		TND	538
18	TND	TND	TND	TND
19	<20	<20	TND	TND
20	TND	<20		TND
21	<20	TND	TND	<20
22	TND	TND	TND	TND
23	<20	TND	<20	32
24	TND	TND	DTG disruption at week 19	
25	TND	<20	TND	TND
26	<20	<20	TND	<20
27	TND			TND
28	TND	TND	TND	<20
29	29	25	<20	46
30	TND	TND	TND	TND
31	TND		<20	TND

HIV RNA is displayed in cps/ml or < 20, when HIV RNA detection > 20 cps/ml. TND=Target not detected. HIV RNA not available in the empty columns. Patient 24 stopped DTG at week 19.