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Review Article

Clinical data and practical experience related to Stribild as an option in patients with HIV infection

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ABSTRACT

Single tablet combination of tenofovir disoproxil fumarate, emtricitabine, elvitegravir and cobicistat [TDF/FTC/EVG/COBI] has been licensed for the use in HIV infected individuals as Stribild®. In treatment naïve subjects high virological efficacy of the regimen was proved. Recently use of this combination has been investigated as the switch option for the virologically suppressed individuals without drug resistance to the components of the compound. In twin studies – STRATEGY-NNRTI and STRATEGY-PI non-inferiority of the switch to TDF/FTC/EVG/COBI was confirmed, discontinuations due to adverse events were infrequent and no emergence of integrase drug resistance was observed. Simplification of the treatment using Stribild is an attractive, effective, safe and well tolerated option which also allows for the optimization of adherence. Elvitegravir-based therapies may be used to replace other antiretroviral regimens in virologically suppressed cases, with no compromise to the virological efficacy of the combination. Use of this novel integrase inhibitor seems to provide durable option for the long-term treatment. In this review we also present a case of the successful treatment optimization with TDF/FTC/EVG/COBI in a patient with poor adherence and protease resistance.

1. Introduction

Virologic failure of antiretroviral treatment is defined as the confirmed viral load >50 copies/ml after 24 weeks of treatment and as such includes both primary virologic failure, when HIV plasma viremia in the antiretroviral treated individual never falls below this threshold or viral load rebound in virologically suppressed individual [1,2]. In these cases evaluation of adherence, drug–drug and drug–food interactions for increased drug turnover and decreased absorbability is necessary and is followed by the resistance testing and treatment modification [3]. Change of cART is guided by the result of the genotypic resistance results with the new treatment usually containing at least one fully active protease inhibitor and one drug not used previously, including an integrase inhibitor and agents from other classes [4].

Current HIV treatment guidelines also provide switch strategies for the stable, virologically suppressed individuals with confirmed HIV-1 viral load <50 copies/ml) [2]. These changes are driven by an array of clinical and patient related factors such as documented toxicity, preemptive switch to avoid long term adverse effects, treatment optimization to minimize drug–drug interactions (existing and potential for the planned concomitant medications) or during pregnancy. Additionally, newer regimens with once daily dosing (STR – single tablet regimens) are being introduced and simplification of multitablet regimens to the single dose ones and BID (bis in die) to QD (quaque die) switches both for patient convenience and optimization of adherence is common [5,6]. It has been shown that once daily regimens are associated with improvement of adherence and treatment acceptance as well as increased probability of the virological failure [7]. Treatment simplification is also desired for the antiretroviral experienced patients to ease the administration burden (e.g. intramuscularly administered fusion inhibitor), increase genetic barrier to resistance development or introduce better tolerated and simpler to administer but effective treatment [5,8–10].

2. Stribild as a novel single tablet treatment option

Single tablet combination of tenofovir disoproxil fumarate (245 mg), emtricitabine (200 mg), elvitegravir (150 mg) boosted with cobicistat (150 mg) [TDF/FTC/EVG/COBI] has been licensed for the use in HIV-1 infected individuals as Stribild® by EMA in May 2013. Approval was based on the registration studies 102 and

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103, where 12% non-inferiority was achieved compared to the comparator – ATV/r + tenofovir/emtricitabine (*GS-US-236-0103* trial) or efavirenz/tenofovir/emtricitabine (*GS-US-236-102* trial) [11–13]. It was subsequently confirmed that high virological efficacy is maintained for the long term – with only 7.9% virologic failures observed throughout 144 weeks of TDF/FTC/EVG/COBI treatment [14].

Use of tenofovir disoproxil fumarate, emtricitabine, elvitegravir and cobicistat in treatment naive individuals has been reviewed previously [15]. This STR has been included in the international and national treatment guidelines as an alternative option for the antiretroviral treatment naive cases; it should also be reminded that elvitegravir is effective against HIV-2 and HIV-0 groups [16,17]. Use of Stribild is recommended in patients with eGFR exceeding 70 ml/min, with no known drug resistance to any of the three antiretroviral components in tenofovir disoproxil fumarate, emtricitabine, elvitegravir and cobicistat, and the agent should be taken with food [13,18,19].

3. TDF/FTC/EVG/COBI as switch option in cART-treated, virologically suppressed individuals

As stated above the reason for the antiretroviral therapy change to elvitegravir containing STR in virologically suppressed individuals might be related to an intent to reduce short and long term adverse events and to reduce the pill burden, which in turn results in the increase in the patient satisfaction [19]. Additional benefits include elimination of partial non-adherence – in case of STR combination of the antiretroviral medicines precludes from selective omission of the components of the combination [7,20,21]. To test if the virologically suppressed patients on NNRTI or PI based regimens, including multitablet ones, would benefit from switch to tenofovir disoproxil fumarate, emtricitabine, elvitegravir and cobicistat in terms of reduction of adverse effects and improvement of satisfaction from the treatment twin studies STRATEGY PI (switch from PI based antiretroviral combination to InSTI) and STRATEGY NNRTI (change from NNRTI containing regimen to InSTI) were carried out [22,23]. Pre-specified aims of both studies were slightly different: STRATEGY PI investigated if the improved adherence and persistence to treatment would outweigh the risk of the virologic failure following treatment simplification to elvitegravir based STR, while STRATEGY NNRTI aimed to observe if the improvement in the neuropsychiatric adverse events of the most commonly used NNRTI – efavirenz – would occur [24,25]. Additionally, patient satisfaction following treatment change to the single tablet once daily was analyzed in these studies.

Both studies were phase 3b, randomized, open-label trials which included participants on combined antiretroviral therapy with plasma HIV-RNA < 50 copies/ml for at least six consecutive months, with full genotypic and phenotypic susceptibility to all administered drugs and Cockroft–Gault estimated glomerular filtration rate (eGFR) $\geq$70 ml/min. For STRATEGY NNRTI patients with M184V, K65R, M41L, L210T mutations, supplemented with D67N, L70A, T215Y/P and L219Q/E/N/R for STRATEGY PI were excluded. Also, any previous exposure to any InSTI was not permitted.

Study participants were allocated in the 2:1 ratio to the switch group which received a coformulation of TDF/FTC/EVG/COBI or the no-switch group to remain of the current PI or NNRTI based regimen. Primary endpoint for STRATEGY NNRTI and PI were proportions of cases with stable viral load $<$50 copies/ml at 48 weeks of treatment as specified by snapshot FDA algorithm. Non-inferiority margin was -12% for the difference in the proportions of individuals with viral load maintained the threshold $<$50 copies/ml using the lower bound of the two-sided confidence interval. Also, if the non-inferiority for the primary endpoint was concluded, and the lower bound of 95% CI was >0, superiority using 0.05 significance level would be analyzed by Fisher's exact test. Both studies were designed with at least 85% power to establish non-inferiority with the pre-specified margin.

Secondary efficacy analyses were based on the proportion of participants with viral load maintained below the above-described threshold using FDA-specified time to loss of virological response (TLOVR) analysis at the 48 weeks of treatment. Additionally, changes in lymphocyte CD4 count, safety and tolerability of the regimens were assessed and described.

The key reasons for the entry into the study, from the participant point of view, were either desire for treatment simplification (83% and 86% for the STRATEGY NNRTI and STRATEGY PI, respectively) or concern about the adverse events of the treatment. Switch groups from PI included participants mostly on atazanavir (42%), darunavir (39%) and lopinavir (17%), while the most common NNRTI switches were from efavirenz (80%) or nevirapine (16%).

In the STRATEGY NNRTI study, the results have shown high frequency of maintained virological suppression (93% and 88% at week 48) in switch and non-switch arms. Obviously, the non-inferiority of the switch was confirmed. When the analysis with the TLOVR algorithm was used to assess the treatment efficacy between the arms, at week 48 the 5.0% difference was observed (92% vs. 87% for the switch vs. non-switch arm, respectively). Increase in the lymphocyte CD4 count was similar regardless the regimen. Despite lack of significant differences in the frequency of virological suppression for age, gender, race or type of NNRTI regimen, factors that slightly, but not significantly, favored the switch included: age $<$40 years, efavirenz as previous treatment option, and being on the first treatment regimen. In comparison, in the STRATEGY PI the simplified, STR containing TDF/FTC/EVG/COBI was also non-inferior at the week 48, but the difference in frequency of virological suppression reached 6.7% [94% vs. 87% (95%CI 0.4–13.7%)] for the switch and non-switch arm, respectively. As this difference was statistically significant ($p = 0.025$) superiority of the switch over the PI based regimen might be assumed. Using the TLOVR algorithm, the difference in the frequency of suppression between the switch and non-switch arm was 91.7% vs. 84.2%, respectively, with significant differences in the virological success rate favoring switch to TDF/FTC/EVG/COBI for the patients $>$40 years of age ($p = 0.044$), male gender ($p = 0.02$), Caucasian origin ($p = 0.037$) and treatment with atazanavir ($p = 0.01$). Resistance was not the issue in either study.

4. Adverse events related to the switch to TDF/FTC/EVG/COBI

It should be noted that adverse events were mostly of the 1st and 2nd grade, and did not exceed 10% of subjects in either study. In STRATEGY NNRTI frequency of side effects was 81% vs. 75% for the switch vs. non-switch group. In the TDF/FTC/EVG/COBI arm headache, nausea, cough and fatigue were significantly more common than among NNRTI-receiving subjects with the frequencies of 10% vs. 3%, 8% vs. 3%, 7% vs. 2% and 5% vs 1%, respectively, but most of them were transient and did not result in treatment discontinuation. Other adverse events with similar prevalence between the groups were: symptoms of respiratory tract infection, nasopharyngitis, diarrhea, insomnia and arthralgia. Key laboratory abnormalities in the switch group included cobicistat-related serum creatinine increase – an effect which is well known and described [26].

Additionally, patient reported outcomes of the treatment indicated that feeling of anxiety, vivid dreams (including nightmares) and insomnia decreased in participants switched off from efavirenz containing cART.