Short communication

Safety, tolerability and pharmacokinetics of enfuvirtide administered by a needle-free injection system compared with subcutaneous injection

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Introduction

Enfuvirtide (ENF; Roche Laboratories, Nutley, NJ, USA; Trimeris, Inc., Morrison, NC, USA) is a first-in-class peptide that inhibits HIV fusion and entry into CD4+ T-cells [1,2]. Studies demonstrated high rates of viral suppression afforded by ENF-containing regimens in triple-class treatment-experienced patients [3–9]. ENF is injected subcutaneously into the upper arm, anterior thigh or abdomen twice daily [2]. The most frequent adverse events (AEs) associated with ENF are injection site reactions (ISRs) [2]. Moreover, patient self-administration and reluctance to use needles are associated with non-adherence with chronic injections. Consequently, the tolerability and utility of subcutaneous ENF might be enhanced by strategies that reduce ISRs and facilitate adherence.

The Biojector 2000 (B2000; Bioject Medical Technologies, Inc., Portland, OR, USA) is a needle-free injection device (NFID) designed for the subcutaneous or intramuscular delivery of vaccines and other injectable drugs [10,11]. Pilot studies demonstrated no change in ENF pharmacokinetics when delivered with the B2000 [12–14] and suggested that ISRs might be improved [15–17]. The WAND study investigated the safety, tolerability, adherence, patient preference and ENF trough concentration (Cţrough) with the use of the NFID compared with a standard needle/syringe (NS) for ENF self-administration in a controlled clinical trial.

Methods

This single-blind, crossover study enrolled treatment-experienced HIV-1-infected adults (age ≥18 years) considered suitable candidates for an ENF-containing regimen. There were no restrictions on viral load, CD4+ T-cell count or prior antiretroviral regimen, except that previous use of ENF and T-1249 was prohibited. This
study was conducted in compliance with the Declaration of Helsinki and all amendments, and adhered to the Guidelines for Good Clinical Practice. Institutional Review Board approval was obtained from each centre.

Participants were randomized (1:1) to use either the NFID or a standard 27-gauge NS to self-administer ENF 90 mg twice daily. After 28 days, participants switched devices. Any ISRs present at the weekly in-clinic evaluations were assessed by severity grade, frequency and body location by a treatment-blinded clinician.

The ISR assessment evaluated pain, erythema, pruritus, induration, ecchymosis and nodules/cysts. The primary endpoint estimated the occurrence of immediate (within <1 h of injection time) or ongoing (began or persisted at ≥1 h post-injection and also present at in-clinic evaluation) painful nodules or induration and was defined as grade 1–3 ongoing pain in association with either grade 3–4 (>25 mm) induration or grade 2–4 nodules/cysts (>20 mm). This endpoint was chosen because, in an analysis of the combined TORO studies, these ISRs were identified as most likely to negatively affect continuation of treatment (Trimeris, Inc., unpublished data).

Participants self-assessed all injection sites and answered questions regarding treatment adherence, ease of use, convenience, preference and pain/discomfort. Wet injections (injectate flowed back out on to the skin after the full dose was ejected) and leak backs (injectate flowed back out on to the skin after the full dose was properly delivered) were recorded.

Pre-dose blood samples were drawn on days 8, 15, 22, 29, 36, 43, 50 and 57 to determine ENF C_\text{trough} using a validated liquid chromatographic method with detection by triple-quadruple mass spectrometry.

On the basis of an expected binary endpoint of 45% with NS, an assumed discordant pairs rate of 27%, and employing a two-sided exact McNemar’s test for paired binary data at a 5% significance level, 40 participants would allow for detection of a statistically significant difference of 23% with 80% probability. The incidence of AEs was similar with the NFID versus 46 participants with the NS (P=0.004), although all experienced at least one ISR with both devices. When considering each ISR sign or symptom separately, the mean number of ISRs per participant was less with the NFID compared with the NS for most signs or symptoms. Across all injection sites, for any sign or symptom, there was a mean of 4.57 ISRs with the NFID compared with 5.43 with the NS. There were significantly lower percentages of participants experiencing grade 2–4 pain and discomfort (P<0.05) and grade 2–4 pruritus (P<0.01) with the NFID than with the NS (Table 1).

By the end of the study, significantly more participants reported improvements in ongoing pain/discomfort (P=0.002) and pruritus (P=0.03) using the NFID compared with the NS (Figure 1) based on the maximum shift in signs and symptoms. Across all injection sites, the mean (±SD) weighted overall ISR severity summary score was lower with the NFID (2.8 ±1.38) compared with the NS (3.6 ±1.65; P=0.02).

In participants with evaluable pharmacokinetic data (n=38) the mean (±SD) C_\text{trough} concentration was similar with the NFID (2,037.7 ±1,130.36 ng/ml) and NS (2,204.4 ±954.17 ng/ml). To compare values, the log-transformed least squares mean and SE were derived (NFID 1,595.7 ±216.4 ng/ml; NS 1,952.8 ±264.8 ng/ml). The ratio of the least squares mean of 0.817 (NFID/NS; 90% confidence interval 0.612–1.092) indicates that these values were not significantly different.

The incidence of AEs was similar with the NFID (22/44; 50%) and the NS (22/46; 48%). Infections were the most frequently reported AEs in the NFID (11/44;
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25\%) and NS (9/46; 20\%) groups. Four participants experienced serious AEs: two (5\%) in the NFID arm (anaemia, haematoma) and two (4\%) in the NS arm (hepatotoxicity, abscess/cellulitis). None was considered ENF-related, although the investigator considered the haematoma to be related to the NFID.

The proportion of abnormal injections was not significantly different between devices. The proportion of wet injections was higher with the NFID (43, 1.9\%) than the NS (4, 0.2\%), whereas leak backs occurred more often with the NS (106, 4.4\%) than the NFID (65, 2.9\%).

Overall, significantly more responding participants stated that they preferred the NFID (22/25; 88\%) over the NS (3/25; 12\%) (P<0.05). Most participants found the NFID easier to use (21/25; 84\%) and more convenient (17/25; 68\%).

### Discussion

ENF-containing regimens provide high rates of virological suppression with immunological improvement for treatment-experienced patients with HIV [4–9,18–20] and ENF is an important part of treatment guidelines for these patients [21,22]. Although ENF is well tolerated with little systemic toxicity, the full benefit of ENF may be limited because of patient reluctance to consider an agent requiring needle self-injection. The NFID may provide an alternative method of administering ENF that reduces ISRs, improving
ENF treatment experience and possibly adherence. It may also diminish the self-injection barriers for many patients and encourage continuation of treatment.

The improved ISR profile with the NFID in this controlled study confirms previous reports that NFID can improve the ENF ISR profile [15–17]. Although the mechanism by which an NFID reduces ISRs is unknown, reductions in ISRs might result from the unique subcutaneous drug dispersion pattern obtained with an NFID compared with the bolus deposition by an NS [12,23,24]. Multidisciplinary approaches to training patients on the proper use of either an NS or the NFID are most likely to produce the best outcomes for adherence and management of ISRs [23].

This controlled comparison between the NFID and an NS showed that, compared with a standard needle, the NFID resulted in significantly fewer painful nodules/indurations, which are frequently associated with limiting ENF use. Moreover, significantly more participants indicated that they were satisfied with, and preferred, the NFID over a standard NS over 4 weeks. These findings confirm observations in previous studies [13–17] showing that needle-free ENF administration was easier to use, reduced injection anxiety, minimized disruption of daily activities and was preferred by patients over a standard NS.

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Disclosure statement

The authors declare no conflicts of interest.

References


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