The Role of Long-Acting Injectables in the Treatment of HIV-1

BACKGROUND

"Combination antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) infection is one of the most important advances in medicine in the past quarter century," said Dr. Judith Currier in her editorial for the *New England Journal of Medicine.*[1] Since ART was introduced in 1996, morbidity and mortality from HIV have decreased dramatically and transformed what was once an acute disease with a poor prognosis into a manageable chronic disease, with life expectancy like those without HIV[2]. U=U is a slogan that seeks to inform the public that when an HIV-positive person is undetectable through taking ART consistently, he or she cannot spread the infection to someone else[3].

In 2018, the Food and Drug Administration (FDA) approved ibalizumab, a humanized monoclonal antibody administered as a biweekly intravenous infusion for HIV for use in treatment-experienced patients with previous failures to ART regimens[4]. The FDA approved it for use with a background ART regimen, and it has provided an alternative treatment option for a select number of patients with documented multidrug resistance. In 2021, the FDA approved cabotegravir extended-release and rilpivirine extended-release, the first complete injectable regimen administered as a monthly injection for the treatment of HIV in patients who are virologically suppressed (HIV-RNA less than 50 copies/ml) with no history of treatment failure or resistance[5].

Long acting, injectable regimens open the door to potential improvement in adherence through not only eliminating the need to take oral pills, but also reducing the self-stigmatization and disclosure concerns that patients with HIV may have. Some long acting injectables are even being studied for HIV prevention[6]. However, clinicians need to be educated about the details of these drugs, how they fit into the current Department of Health and Human Services (DHHS) guidelines, and to identify the patient populations who are best suited for them.

EDUCATIONAL ANALYSIS

Gap 1: Clinicians may be unaware of long acting injectables that the FDA approved for the treatment of HIV.

Learning Objective 1: Describe long acting injectables that the FDA has approved to treat HIV.

<u>Ibalizumab</u>

Ibalizumab is approved for the treatment of HIV-1 in patients who have been on multiple antiretrovirals in the past, developed resistance to these medicines, and are currently experiencing failure with their current HIV treatment[4]. Ibalizumab is a humanized immunoglobulin monoclonal antibody that binds to CD4 cells, thereby blocking HIV-1 entry.

It's administered as a single loading dose of 2000 mg followed by a maintenance dose of 800 mg via IV infusion, given over 15 to 30 minutes, every 2 weeks by a healthcare provider at home, an infusion center or the healthcare provider's office[4].

Clinical trial TMB-301 enrolled 40 heavily treatment-experienced HIV-1 positive patients displaying multidrug resistance. Participants had HIV RNA levels greater than 1000 copies/mL and demonstrated resistance to at least one antiretroviral medication from each of three classes of antiretroviral medications[4]. The study had a control period (days 0-6) to observe baseline HIV viral load, functional monotherapy period (days 7-13) to establish the virologic activity of ibalizumab, and a maintenance period (day 14-25) that included an optimized background regimen, to establish the safety and durability of ibalizumab[4].

The primary endpoint was the proportion of patients achieving a $0.5\log_{10}$ or greater decrease in viral load between the control and functional monotherapy periods. The results showed 83% vs 3% ($p < 0.0001$) of patients in the functional versus control group achieving a 0.5log10 decrease in viral load. In addition, 43% of patients achieved a viral load less than 50 copies/ml and 50% of patients achieved a viral load of less than 200 copies/ml. The most common side effects reported in at least 5% of patients were diarrhea, dizziness, nausea, and rash[4].

<u>Cabotegravir and Rilpivirine</u>

In 2021, the FDA approved a combination product of cabotegravir and rilpivirine for the treatment of HIV-1 in patients with undetectable HIV levels (HIV-1 RNA less than 50 copies/ml), on stable antiretroviral therapies, with no history of resistance or treatment failure. Considered a complete regimen, cabotegravir and rilpivirine is given orally (cabotegravir 30 mg daily and rilpivirine 25 mg daily) for at least 28 days to assess tolerability then replaced by a one-time initiation of two intramuscular (IM) gluteal injections (opposite sides or 2 cm apart) of long acting cabotegravir 600 mg and long acting rilpivirine 900 mg. One month later, the continuation IM injections of long-acting cabotegravir 400 mg and long-acting rilpivirine 600 mg are given and continued monthly. All shots must be delivered by a healthcare provider. There is dosing flexibility with a target treatment date determined in advance and a 7-day window before and after the target treatment date is allowed[5].

"I think the long-acting formulations definitely have the potential to improve adherence," says Elena Bekerman, a senior research scientist.[6] Adherence plays a crucial role in the effectiveness of HIV treatment. Although IM cabotegravir and rilpivirine eliminates the burden of daily pill taking, patients selected for this regimen should agree to be adherent to the initial pills (for the first month) and monthly injections (every month thereafter). For patients who miss scheduled injections, the healthcare provider needs to reassess whether resuming therapy remains appropriate. Dosing recommendations for missed injections are available for prescribers[5].

FLAIR and ATLAS phase 3 clinical trials evaluated the safety and efficacy of cabotegravir and rilpivirine. In FLAIR, 629 antiretroviral naïve patients were given dolutegravir/abacavir/lamivudine (or dolutegravir plus two other NRTIs if patients were HLA-B*5701 positive) for 20 weeks then 566 undetectable patients (HIV-1 RNA less than 50 copies/ml) were randomized to stay on their current regimen or receive oral

cabotegravir/rilpivirine (for 28 days) followed by long-acting IM cabotegravir/rilpivirine for 48 weeks. ATLAS enrolled 616 patients with HIV-1 who were undetectable (HIV-RNA less than 50 copies/ml) for at least 6 months on 2 NRTs plus a 3rd agent. Half of the patients then remained on their antiretroviral regimen and half of patients switched to oral cabotegravir/rilpivirine (for 28 days) followed by long acting cabotegravir and rilpivirine for 48 weeks[5].

The primary endpoint for both studies was the proportion of patients with HIV-RNA greater than 50 copies/ml at 48 weeks. Both studies excluded patients with concomitant hepatitis B, patients with moderate to severe hepatic impairment and women who were or planning to become pregnant or breastfeed. The results showed a difference of 0.2% (CI -1.4%, 1.7%) between cabotegravir/rilpivirine and the current antiretroviral regimen for the primary endpoint of HIV-1 RNA greater than 50 copies/ml. The secondary endpoint was HIV-1 RNA less than 50 copies/ml at 48 weeks. A total of 93% of patients on the cabotegravir/rilpivirine group achieved this and 94% of the current antiretroviral regimen achieved this. These results demonstrated that cabotegravir/rilpivirine was non-inferior to the standard oral antiretroviral regimen in virologically suppressed patients. The most common side effects reported were injection site reactions, the majority of which were mild to moderate[5].

"*I love it because I don't have to take a daily medication, so that's just one less thing on my plate that I have to worry about… I definitely feel there's less pressure*. *I like the injection because it's not a daily, in my face, I have to do this"*. –U.S., Female trial participant.[7]

At week 48, patients were asked a survey question assessing their preference to the IM cabotegravir/rilpivirine regimen or oral antiretroviral regimen. 9 out 10 survey participants indicated they preferred IM cabotegravir/rilpivirine to the current antiretroviral regimen.[5]

Gap 2: Clinicians may be unaware of the role in therapy of long acting injectables in the DHHS guidelines.

Learning Objective 2: Discuss the DHHS guidelines and the role of long acting injectables in the treatment of HIV.

Managing the Treatment-Experienced Patient

For the treatment experienced patient with HIV-1, determination of virologic failure should include drug and food interactions, drug tolerability, assessment of adherence, viral load and CD4 cell count trends over time, ART history and prior and current drug-resistance test results[2]. Virologic failure is defined as consistent HIV RNA level greater than 200 copies/ml and is linked to accumulation of drug-resistance mutations[4]. Challenges with adherence and drug intolerance/toxicity are key contributors to virologic failure as is the presence of preexisting drug resistance[2].

The DHHS guidelines recommend starting patients with virologic failure on a new regimen of at least two, but preferably three fully active agents. Two agents may be sufficient if one has a high

resistance barrier (e.g., dolutegravir or boosted darunavir) however, three is preferred if no high resistance barrier drug is available[2].

For patients with HIV RNA greater than 1000 copies/ml and identified drug resistance, clinicians should modify their regimens as soon as possible to avoid progressive accumulation of resistance mutations. Virologic response is greater for those with lower HIV RNA and higher CD4 counts, therefore it's critical to change drugs quicky before viremia gets worse or CD4 declines[2].

Patients who have multidrug resistance and failed more than two regimens have limited treatment options. These patients with ongoing detectable viremia may be candidates for Ibalizumab and could benefit from its novel mechanism of action[4].

Enhancing ART in the Setting of Virologic Suppression

There are several reasons to change ART regimens in the setting of virologic suppression including a desire to simplify the regimen by reducing pill burden and dosing frequency and minimize potential stigma or disclosure concerns related to taking daily oral medications, to name a few[2].

Intramuscular cabotegravir and rilpivirine is an optimized option for patients who are involved in their healthcare, undetectable (HIV-1 RNA less than 50 copies/ml) on oral therapy for three to six months and who agree to make the frequent clinic visits needed to receive the injectable drug[2]. Furthermore, these patients should have no concomitant hepatitis B infection, and no history of drug resistance or virologic failures, are not pregnant or seeking to become pregnant, and are not on medications that can interact with cabotegravir and rilpivirine (e.g, certain anticonvulsants, antimycobacterials, dexamethasone, St. John's Wort, and certain macrolide antibiotics)[5].

Gap 3: Clinicians may be unaware of the limitations of long acting injectables.

Learning Objective 3: List the concerns and opportunities for further investigation with long acting injectables.

Although long acting injectables show great promise, there are still areas of concern that warrant additional investigation and consideration. In general, both ibalizumab and cabotegravir/rilpivirine require administration by a healthcare professional; patients cannot self-administer and must have the transportation needed to make these visits[7] (although ibalizumab can be administered at home by a healthcare provider[4]). This can be challenging for patients with limited transportation options.

Furthermore, clinics will need to add on this additional administration visit to normal six-month interval visits. Given the additional logistic challenges, alternative delivery sites could be investigated (e.g., pharmacies, minute-clinics, community-based organizations, and mobile vans).[7]

With adherence playing a crucial role in the efficacy of these long acting injectables, drug resistance and mutations could develop from patients who stop receiving injections and fail to switch to oral medications[7]. Concentrations of cabotegravir/rilpivirine are detectable in the blood for at least 12 months after the last dose[2]. Guidance exists on what to do in the event the patient has a planned or unplanned missed dose within the 7-day treatment window[5]. If the patient misses a dose beyond the 7-day treatment window, clinicians should re-evaluate whether the patient remains an appropriate candidate for injectable therapy.

Another potential gap that could be addressed with continuing education is describing these medications in patient populations that were excluded from clinical trials including, pregnant women, children and adolescents, minorities, people with low-income, and patients with comorbidities such as hepatitis B[1].

CONCLUSION

Treatment for HIV took a giant step forward with the advent of long acting injectables, eliminating the need for daily oral medication. To gain the most from these new treatment regimens, clinicians need to become fully acquainted with the details of ibalizumab and long acting cabotegravir with rilpivirine, renew their working knowledge of the DHHS guidelines with an emphasis on how these drugs fit into the guidelines, understand the limitation of these drugs, and adjust treatment choices to individual patient needs to optimize therapeutic outcomes and patient satisfaction.

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