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Antibody-based strategies in HIV therapy

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ABSTRACT

Antibody-based strategies have been introduced for a number of disease states, but represent a novel approach in the management of human immunodeficiency virus (HIV). Ibalizumab and leronlimab are monoclonal antibodies with unique mechanisms as a CD4-directed post-attachment inhibitor and a C-C chemokine receptor type 5-directed inhibitor, respectively. These antibody-based strategies are generally well tolerated, have a favourable pharmacokinetic profile allowing for less-frequent dosing, and have a high barrier to resistance. Ibalizumab is currently approved by the US Food and Drug Administration (US FDA) for management of multi-drug-resistant (MDR) HIV infection in patients who are failing their current regimens. Clinical data demonstrated impressive antiretroviral activity with ibalizumab among a complex HIV population in combination with an optimized background regimen, where limited therapeutic options exist. To date, leronlimab has not been granted approval by the US FDA, but has been designated fast-track status. Leronlimab is being studied as a maintenance monotherapy agent in virologically suppressed patients, as well as for treatment of MDR HIV infection in patients who are failing their current regimens. Currently available data in both of these potential areas appear promising for leronlimab. The mechanism of action, pharmacokinetic profile, efficacy and safety of these novel antibody-based strategies represent an advance in the management of HIV. Future studies and post-marketing experience will further determine longer-term clinical efficacy, safety and resistance data for ibalizumab and leronlimab.

1. Introduction

Antiretroviral therapy (ART) has considerably improved the prognosis of patients infected with human immunodeficiency virus (HIV). However, approximately 95% adherence to ART is required to maintain viral suppression, decrease opportunistic infections, and minimize antiretroviral resistance [1]. While ART has generally become simpler, adherence can still be challenging due to complex dosing regimens, frequent administrations, drug interactions and dietary considerations [2]. As such, there is a need for antiretrovirals with less-frequent dosing and higher barriers to resistance [3]. Furthermore, several patients with complex ART regimens are still unable to meet viral suppression due to multi-drug-resistant (MDR) HIV, and are more vulnerable to treatment failure [4], worse clinical outcomes and increased mortality [5–7].

One area of interest for these niches in HIV therapeutics is the development of antibody-based strategies [8]. Several monoclonal antibodies already exist for treatment of multiple diseases, including autoimmune diseases, cancers and infectious diseases. Antibody-based strategies for HIV offer a unique mechanism of action, decreased potential for development of acquired resistance, and improved potential safety profile, especially for MDR HIV infection where limited effective and well-tolerated antiretrovirals exist [9]. This review highlights various antibody-based strategies and their role in HIV management with a focus on ibalizumab and leronlimab. Literature searches were performed using PubMed, EMBASE and Google Scholar. Search terms included 'antibody', 'monoclonal antibody', 'HIV', 'multidrug resistant HIV', 'ibalizumab', 'leronlimab' and 'PRO 140' to identify peer-reviewed publications as of 20 September 2020. Abstracts, posters and press releases were utilized if data were not yet available as published articles. A brief comparative summary of ibalizumab and leronlimab is displayed in Table 1.

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Table 1
Brief comparative summary of ibalizumab and leronlimab

	Classification	Mechanism of action	US FDA approval status	Indication/target population	Dosing	Adverse effects
Ibalizumab	Humanized immunoglobulin G4 monoclonal antibody	CD4 post-attachment inhibitor	Approved in 2018	Treatment of MDR HIV-1 infection in combination with other antiretrovirals in adults who are failing their current regimen	2000 mg IV once (LD) followed by 800 mg IV every 14 days (MD)	Generally well tolerated
Leronlimab (PRO 140)	Humanized Immunoglobulin G4 monoclonal antibody	CCR5 inhibitor	Not approved; granted fast-track status	– Treatment experienced patients in combination with OBR and CCR5-tropic MDR HIV – Monotherapy maintenance of viral suppression	350 mg subcutaneously every 7 days	Generally well tolerated

CCR5, C-C chemokine receptor type 5; HIV, human immunodeficiency virus; IV, intravenous; LD, loading dose; MD, maintenance dose; MDR, multi-drug resistant; OBR, optimized background regimen; US FDA, US Food and Drug Administration.

2. Ibalizumab

Ibalizumab is currently the only monoclonal antibody approved by the US Food and Drug Administration (US FDA) for HIV, specifically in combination with other antiretrovirals for heavily-treatment-experienced adults who are failing their current regimen [10]. Ibalizumab is a recombinant humanized immunoglobulin G (IgG) 4 monoclonal antibody that exhibits a unique mechanism of action as a CD4 post-attachment inhibitor [11,12]. Traditionally in HIV infection, the HIV envelope glycoprotein 120 (gp120) binds to CD4 cell extracellular domain 1, which leads to a conformational shift in V1 and V2 loops that subsequently exposes the V3 loop and causes a shift from a closed state to an open state [13]. However, ibalizumab binds to amino acid positions within domains 1 and 2 of the CD4 cell, which induces steric hindrance and prevents the aforementioned conformational changes between gp120 and the CD4 cell to ultimately prevent viral fusion [11]. The activity of ibalizumab is independent of C-X-C chemokine receptor type 4 (CXCR4)- and C-C chemokine receptor type 5 (CCR5)-tropic strains because of its unique steric hindrance mechanism.

2.1. Pharmacokinetics, pharmacodynamics and dosing

Ibalizumab is administered as an intravenous (IV) loading dose of 2000 mg followed by a maintenance dose of 800 mg IV every 14 days [10,12]. Following the 2000-mg loading dose, the maximum concentration was 567 μg/mL. Following administration of the 800-mg maintenance dose every 14 days, the mean concentration was ≥30 μg/mL and demonstrated a time above the EC_{85} (i.e. concentration required for ≥85% receptor occupancy) of 100% throughout the dosing interval [12]. Ibalizumab appears to demonstrate a linear, dose-dependent exposure [14]. The estimated half-life of ibalizumab following maintenance dosing is approximately 72–84 h [14,15], which is considerably less than the 2–3 week half-life of IgG [14]. This difference in half-life is due to different clearance mechanisms such as internalization or shedding for the ibalizumab–CD4 receptor complex [16].

In the phase III study, 97% and 81% of subjects exhibited at least 85% CD4 cell receptor occupancy following the approved dosing regimen at day 21 and week 25, respectively [12]. Regardless of baseline resistance profiles, ibalizumab exhibited a similar maximal percentage of inhibition compared with other antiretrovirals, including nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase strand transfer inhibitors, enfuvirtide and maraviroc [17].

While less-frequent dosing may be advantageous, missed doses may compromise the effectiveness of ibalizumab. If a maintenance dose is missed by ≥3 days, a loading dose should be re-administered immediately, followed by maintenance dosing every 14 days thereafter. No specific studies have been performed to assess the impact of hepatic or renal dysfunction on the pharmacokinetics of ibalizumab, but these are not expected to alter such parameters [10]. Furthermore, no specific drug interaction studies have been performed, but interactions are not anticipated given the mechanism of action of ibalizumab.

2.2. Clinical data

Ibalizumab was studied in two phase I [14,15], two phase II (TNX-355.03 and TMB-202) [18,19] and two phase III (TMB-301 and TMB-311) [12] clinical trials. Phase II and phase III clinical trial data are summarized in Table 2.

TNX-355.03 was a phase IIa, randomized, double-blind, placebo-controlled study to investigate the effect of two ibalizumab dosing strategies on HIV RNA concentrations at weeks 24 and 48 (Table 2) [18]. In addition to an optimized background regimen (OBR) guided by antiretroviral resistance testing, subjects were randomized to receive: (1) 15 mg/kg every 2 weeks (n=28); (2) 10 mg/kg every week for nine doses followed by every 2 weeks (n=27); or (3) placebo (n=27). Both ibalizumab dosing regimens achieved significant reductions in HIV RNA at 24 and 48 weeks. The mean CD4 count increased from 223 cells/mm^3 to 274 cells/mm^3 (P=0.016) and from 299 cells/mm^3 to 347 cells/mm^3 (P=0.031) at 48 weeks for the 15 mg/kg IV every 14 days regimen and for the loading dose followed by maintenance dosing regimen, respectively.

TMB-202 was a phase IIb, randomized, double-blind, dose–response study to investigate two ibalizumab dosing strategies plus OBR on undetectable viral load achievement at week 24 (Table 2) [19]. In addition to OBR, subjects were randomized to receive ibalizumab 800 mg IV every 14 days (n=59) or 2000 mg IV every 4 weeks (n=54). The mean reduction in HIV RNA from baseline, percentage of subjects achieving a 1.0 $\log_{10}$ reduction in HIV RNA, and mean increase in CD4 were similar between the two regimens at week 24. Pharmacokinetic investigations led to the dosing regimen used in the phase III study.

TMB-301 was a phase III, single-group, open-label study to evaluate ibalizumab on HIV RNA decline in 40 subjects with MDR HIV-1 infection who were failing their current ART regimen (Table 2) [12]. This study was conducted across three time periods: control (days 0–6), where subjects continued their prior ART; functional monotherapy (days 7–13), where subjects received ibalizumab 2000 mg and continued their prior ART; and maintenance (day 14 to week 25), where subjects started an OBR and received ibalizumab 800 mg every 14 days starting on day 21. Baseline mean HIV RNA was >100 000 copies/mL; 17 (43%) subjects had CD4 <50 cells/mm^3; and documented resistance to all drugs in

Table 2
Summary of clinical trial data for ibalizumab and leronlimab

Study	Primary outcome	Study population	Efficacy results[c]	Safety results[c]
TNX-355.03[a] (phase II)	Mean change in HIV RNA from baseline to weeks 24 and 48	82 subjects who received ART from three drug classes with baseline HIV RNA ≥10 000 and CD4 ≥50	– Mean reduction in HIV RNA of approximately 1.0 $\log_{10}$ copies/mL at 24 and 48 weeks compared with baseline for both dosing regimens – Most significant reduction in HIV RNA occurred with LD regimen at 48 weeks (1.16 $\log_{10}$; P<0.001)	NR
TMB-202[a] (phase II)	Proportion of subjects with undetectable viral load at week 24 (HIV RNA <50)	113 subjects with HIV RNA ≥1000 and decreased susceptibility to ≥NRTI, NNRTI or PI at baseline	– Undetectable HIV RNA was achieved in 26 (44%) subjects receiving 800 mg IV every 14 days and 15 (28%) subjects receiving 2000 mg IV every 4 weeks (P=0.160)	– 15 serious AE (none related to ibalizumab) – Treatment-emergent AE: 12% (rash), 8% (diarrhoea), 7% (headache, URTI, nausea), 6% (fatigue)
TMB-301[a] (phase III)	Proportion of subjects with ≥0.5 $\log_{10}$ reduction in HIV RNA from baseline (day 7) to day 14	40 subjects who received ART for ≥6 months, HIV-1 RNA >1000 on ART for ≥8 weeks, and resistance to at least one drug in at least three ART classes	– 33 (83%) subjects achieved a reduction in HIV RNA of ≥0.5 $\log_{10}$ at day 14 compared with baseline (P<0.001) – 17 (43%) subjects had HIV RNA <50, 20 (50%) subjects had HIV RNA <200, and mean increase in CD4 was 62 at week 25 – Seven (18%) subjects had virologic failure at week 25	– 32 (80%) of subjects developed at least one AE, but 87% were non-severe – Most common: 20% (diarrhoea) – Four deaths unrelated to ibalizumab – One discontinuation (IRIS)
TMB-311[a] (phase III)	Proportion of subjects with HIV RNA <50 and <200 at 48 weeks	27 of 31 subjects who completed TMB-301 and continued maintenance dosing	– 16 (59%) and 17 (63%) subjects maintained HIV RNA <50 and <200, respectively	No new or unanticipated safety concerns
CD01[b] (phase IIb)	Time to virologic failure (2 consecutive HIV RNA ≥400) after initiation of leronlimab monotherapy at 12 weeks	41 included subjects with HIV RNA <50 for at least 6–12 months and on a stable ART regimen	– Mean 51.3 days to virologic failure (range 28–78 days) – Virologic suppression rate of 56% at 12 weeks – Subjects who failed had a higher IC_{90} at baseline than those who did not fail (10.8 vs. 6.7 μg/mL)	– 11 mild and transient injection site reactions identified as definitely and probably related AEs (no discontinuations) – Two serious AEs deemed unrelated to leronlimab
CD01 extension[b]	Extension of CD01 through 160 weeks	16 virologically suppressed subjects included from CD01	– Five subjects experienced virologic failure (no resistance emerged) – One subject withdrew consent – Ten subjects remained suppressed for 47–129 weeks	
CD03[b] (phase IIb/III)	Virologic failure at 28 weeks on monotherapy (two consecutive HIV RNA >200)	156 virologically suppressed subjects enrolled in part 1	– OR=4.43 for virologic response rates with 525 mg (n=74) vs. 350 mg (73) from 147 subjects (interim finding) – 92% (24/26) subjects achieved viral suppression with 700 mg up to 12 weeks – Majority of viral load breakouts due to incidents that increase T cells	– Frequency and severity of injection site reactions were similar between three dose groups
CD02[b] (phase IIb/III)	Proportion of subjects with ≥0.5 $\log_{10}$ reduction in HIV RNA at end of 1 week	52 subjects with HIV RNA ≥400 and resistance to three ART classes or two ART classes with limited agents available	– Reduction of ≥0.5 $\log_{10}$ from baseline in HIV RNA at end of 1 week with leronlimab compared with placebo (P=0.0032) – 81% and 92% of subjects demonstrated HIV RNA <50 and <400 at 25 weeks, respectively	– No serious AEs related to leronlimab reported

AE, adverse effects; ART, antiretroviral therapy; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome; IV, intravenous; LD, loading dose; NR, not reported; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; URTI, upper respiratory tract infection.

[a] Represents clinical trial data for ibalizumab.

[b] Represents clinical trial data for leronlimab.

[c] Efficacy and safety results are summarized in brief.

at least one, two, three or four ART classes was 85%, 73%, 50% and 33%, respectively. Five (13%) subjects had documented resistance to all approved antiretrovirals, and 17 (43%) subjects required fostemsavir, an investigational antiretroviral, to create an OBR. While 40 subjects were included in the intention-to-treat analysis, 31 completed the study. TMB-311 was a phase III clinical trial to allow subjects who completed TMB-301 to continue ibalizumab for 48 weeks (Table 2) [20]. All 15 subjects with HIV RNA <50 copies/mL at the end of TMB-301 maintained undetectable viral loads at 48 weeks. A subgroup analysis of TMB 301/311

also demonstrated comparable and durable virologic efficacy regardless of the number of active agents among subjects who received ibalizumab in combination with one or two fully active agents [21].

2.3. Resistance

Resistance to ibalizumab may develop through decreased interactions between HIV gp120 and CD4 cells that minimize steric hindrance and the therapeutic effect of ibalizumab [22,23]. Specifically, reduced expression or loss of N-linked glycosylation sites (PNGS) in variable region 5 of gp120 is considered the primary mechanism. Loss of PNGS was the primary modification associated with reduced ibalizumab susceptibility in TMB-301; however, a reduction in the maximal percentage of inhibition from baseline was not predictive of virologic failure or rebound [20].

Resistance has been observed to develop within 1–2 weeks in patients receiving ibalizumab monotherapy [24]. Decreased virologic response and concern for resistance has also been noted with even one missed infusion in subjects who received 2000 mg every 4 weeks, emphasizing the importance of adherence [19]. Currently, there are no commercially available resistance testing methods for patients with suspected resistance to ibalizumab [9].

Cross-resistance between ibalizumab and other antiretrovirals, particularly entry inhibitors such as maraviroc or enfuvirtide, has not been reported [11]. One subject developed anti-ibalizumab antibodies in TMB-202, but titres were low and drug efficacy was not impacted [19]. No other studies observed development of anti-ibalizumab antibodies [12,15].

3. Leronlimab

While not FDA-approved at present, leronlimab (previously known as PRO 140) is a humanized IgG4, kappa monoclonal antibody directed towards CCR5 that has re-emerged as a potential novel agent for HIV treatment [25]. Leronlimab is only considered in patients with CCR5 tropic virus; however, the majority of patients harbour this HIV tropism. Leronlimab has a unique mechanism of action by binding to CCR5 with high affinity, and ultimately inhibiting HIV entry into CD4 cells [25]. Leronlimab binds specifically to the N-terminus and extracellular loop 2 domain of CCR5 to interfere with the final phase of viral binding to the CD4 cell [26]. Interestingly, leronlimab is active against maraviroc-resistant strains and has been shown to be synergistic with maraviroc [27,28]. Leronlimab is also being studied in other disease states, including metastatic triple-negative breast cancer, metastatic colorectal cancer, non-alcoholic steatohepatitis, graft-versus-host disease and coronavirus disease 2019.

3.1. Pharmacokinetics, pharmacodynamics and dosing

Leronlimab is administered as a subcutaneous injection every week based on its favourable pharmacokinetic profile [29]. The mean half-life of leronlimab after multiple subcutaneous doses is 3.4 and 3.7 days at 162 mg and 342 mg, respectively [29]. Leronlimab metabolism is mediated through a saturable antigen clearance mechanism, and thus, no dose adjustments are needed in patients with hepatic or renal dysfunction [25]. Furthermore, drug–drug interactions are not anticipated. After a single 5 mg/kg IV dose (350 mg for a 70-kg patient), CCR5 receptor coating was observed for >60 days [30]. More than 85% of receptor occupancy was observed through day 29 at 5 and 10 mg/kg, and 81% was observed at day 43 of 10 mg/kg [31]. Specific leronlimab dosing regimens are still being investigated.

3.2. Clinical data

Leronlimab has been studied in nine clinical trials to date, including four phase I studies (including unpublished data) [25,32], three phase II studies [29–31] and two phase III extension studies [33,34]. Leronlimab has been granted fast-track status by the US FDA. Phase IIb and phase III clinical trial data are summarized in Table 2, yet partial data from these studies continue to emerge through abstracts, conference presentations, press releases and published manuscripts.

CD01 is a phase IIb, randomized, open-label study to investigate leronlimab monotherapy to maintain viral suppression for >24 months [30]. Leronlimab 350 mg was administered subcutaneously every week for 12 weeks in combination with current ART. After 1 week, combination ART was discontinued, and leronlimab was continued as monotherapy to avoid the possibility of viral rebound. Subjects who experienced viral rebound (HIV RNA >400 copies/mL on two consecutive draws ≥3 days apart) restarted their original ART. Forty-three subjects were enrolled, but two subjects were removed because they had mixed tropism prior to receipt of leronlimab [35]. Thus, 41 subjects were studied through three cohorts: cohort 1 (n=11), cohort 2 (n=28) and cohort 3 (n=2). More than half of the enrolled subjects maintained virologic suppression at 12 weeks. Sixteen subjects from cohorts 2 and 3 entered the CD01 extension study for follow-up over 160 weeks.

Similar to CD01, CD03 is an ongoing phase IIb/III, randomized, open-label study to investigate leronlimab monotherapy at doses of 350 mg, 500 mg or 700 mg weekly for 48 weeks [30,36]. In part 1, 156 subjects received 350 mg subcutaneously every week. In part 2, 147 subjects received 350 or 525 mg in a 1:1 ratio as a randomized, controlled, two-arm study. In part 3 (ongoing), 47 subjects are randomized to receive 525 or 700 mg in a 1:1 ratio. More than 90% of subjects who received 700 mg achieved viral suppression without any increased safety risk for up to 12 weeks, compared with 71% and 44% with 525 mg and 350 mg, respectively [36]. Central nervous system and genitourinary substudies are also included to evaluate leronlimab concentrations and HIV RNA at these sites.

CD02 was a randomized, double-blind, placebo-controlled trial that investigated the efficacy, safety and tolerability of leronlimab in treatment-experienced HIV subjects [37,38]. Leronlimab 350 mg or placebo was added to the failing ART for 1 week, followed by the single-arm, open-label treatment period of leronlimab in combination with an OBR for 25 weeks. Leronlimab 350 mg was administered subcutaneously every week. Of 52 subjects enrolled, 47 completed the 25-week period, with 40 subjects who requested to continue receiving leronlimab in an extension study. Several of these subjects have maintained viral suppression for >2 years.

3.3. Resistance

The primary mechanism of resistance is emergence of CXCR4 or mixed tropism. However, this observation has been rare. To date, five subjects have reported CXCR4 tropism shift, but three had mixed tropism present at baseline among the 170 subjects who had tropism data available [3,25,29,31]. One subject had mixed tropism at day 8 but CCR5 tropism at all other study time points [25]. Additionally, two subjects had temporary emergence of CXCR4 tropism, which later returned to CCR5 tropism at study completion [31].

4. Discussion and future directions

Ibalizumab and leronlimab are novel monoclonal antibodies with unique mechanisms of action as a CD4-directed post-attachment inhibitor and a CCR5-directed inhibitor, respectively

[3,9]. Both agents are generally well tolerated, have less-frequent dosing, lack drug interactions and have a high barrier to resistance, making them intriguing options for niche roles in HIV management. Antibody-based strategies may also have a role in capacities other than MDR HIV management and maintenance monotherapy, including pre-exposure prophylaxis, post-exposure prophylaxis and mother-to-child transmission. There is also interest in the combined use of ibalizumab and leronlimab, particularly for treatment-experienced patients [35].

Ibalizumab is currently the only monoclonal antibody approved for treatment of HIV specifically in patients with MDR HIV who are failing their current regimen [9]. This patient population is highly complex, and limited options are available, as represented in the patient population studied in TMB-301 [12]. Fortunately, ibalizumab was well tolerated from a safety perspective. While ibalizumab is available as an IV infusion, administration can occur in multiple settings, and alternative routes of administration such as intramuscular and subcutaneous injections have been explored [24,39]. As with most monoclonal antibodies, ibalizumab is costly, with an estimated wholesale annual cost of approximately $120 000 [40]. A cost-effectiveness analysis was performed to compare ibalizumab plus OBR with OBR alone [41]. Based on these results, ibalizumab will substantially increase survival when effective for patients with MDR HIV lacking other treatment options. Interestingly, the addition of ibalizumab to an OBR was not found to be cost-effective even with 100% efficacy; however, the number of patients eligible to receive ibalizumab is generally considered to be low, and the overall budget impact is thought to be relatively small. Nonetheless, ibalizumab remains a salvage option in a challenging MDR HIV patient population.

Leronlimab has been studied as maintenance monotherapy in virologically suppressed patients, as well as for treatment of MDR HIV in combination with other ART [3]. Unlike ibalizumab, leronlimab is primarily being studied as a subcutaneous injection. As maintenance monotherapy, leronlimab demonstrated promise in maintaining virologic suppression, especially at higher doses, without compromising safety. In this capacity, leronlimab offers a potential long-acting, monotherapy maintenance regimen. Similar to ibalizumab, leronlimab has also demonstrated notable virologic suppression results in treatment-experienced patients with MDR HIV who have limited options available. Leronlimab has received fast-track designation, but is yet to be approved by the US FDA.

Although more clinical data remain to be revealed by future studies and post-marketing experience, ibalizumab and leronlimuab represent novel antibody-based strategies for HIV management with roles in multiple potential capacities where treatment options are needed critically.

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