Drugs (2020) 80:189–196
https://doi.org/10.1007/s40265-020-01258-3

ADIS DRUG EVALUATION

Ibalizumab: A Review in Multidrug-Resistant HIV-1 Infection

Hannah A. Blair[1]

Published online: 22 January 2020

Abstract

Ibalizumab (Trogarzo®; ibalizumab-uiyk) is the first monoclonal antibody to be approved for the treatment of HIV-1 infection. As a CD4-directed post-attachment inhibitor, ibalizumab blocks HIV-1 entry into CD4 cells while preserving normal immune function. Ibalizumab, in combination with other antiretroviral(s), is indicated in the USA for the treatment of heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen, and in the EU for the treatment of adults infected with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen. In the pivotal phase III TMB-301 trial, ibalizumab significantly reduced the viral load 7 days after being added to a failing antiretroviral regimen. Almost half of all patients achieved an undetectable viral load after 24 weeks of treatment with ibalizumab plus an optimized background regimen, with virological suppression maintained over the longer term (up to 96 weeks) in an expanded access protocol. The drug was generally well tolerated in clinical trials. Although additional studies and long-term post-marketing data are needed to fully determine its efficacy and safety, ibalizumab represents a valuable and much needed treatment option for patients with multidrug-resistant HIV-1 infection.

Ibalizumab: clinical considerations in multidrug-resistant HIV-1 infection

First-in-class CD4-directed post-attachment HIV-1 inhibitor

Demonstrates potent antiviral activity 7 days after being added to a failing antiretroviral regimen

Provides sustained virological suppression when administered in combination with an OBR

Generally well tolerated

Enhanced material for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.11540427.

The manuscript was reviewed by: ***A. Calmy***, Infectious Disease Division, Geneva University Hospitals, Geneva, Switzerland; ***O. Kirk***, Department of Infectious Diseases, University of Copenhagen, Copenhagen, Denmark; ***M. Liedtke,*** University of Oklahoma, College of Pharmacy, Oklahoma City, OK, USA.

✉ Hannah A. Blair
demail@springer.com

[1] Springer Nature, Mairangi Bay, Private Bag 65901, Auckland 0754, New Zealand

1 Introduction

Advances in antiretroviral therapy (ART) over the years have greatly improved outcomes for patients with HIV-1 infection, with the disease now considered to be a manageable (albeit chronic) condition [1]. Standard combination ART regimens generally comprise three active drugs from two or more drug classes [1]. Most initial regimens include two nucleoside reverse transcriptase inhibitors (NRTIs) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI) or an integrase strand transfer inhibitor (INSTI) [1, 2]. Despite the proven benefits of ART, the development of resistance to available therapies is a continuing concern [3]. Patients with multidrug-resistant HIV-1 infection are susceptible to treatment failure, have worsened clinical outcomes and have a higher risk of death than other HIV-1-infected patients [4, 5]. Therefore, the development of new antiretroviral agents with a high genetic barrier to resistance is crucial [3].

The entry of HIV-1 into susceptible target cells (mainly CD4+ lymphocytes) is a complex multistep process involving viral attachment, co-receptor binding, and fusion [6, 7]. A number of HIV-1 entry inhibitors with different mechanisms of action have been developed to interact with specific steps in the entry process [7], thereby inhibiting HIV-1 from entering and infecting the immune cells [6]. Entry inhibitors

currently available for the treatment of HIV-1 infection include the CCR5 co-receptor antagonist maraviroc and the fusion inhibitor enfuvirtide [6, 7].

Ibalizumab (Trogarzo®; ibalizumab-uiyk) is a first-in-class CD4-directed post-attachment HIV-1 inhibitor and the first monoclonal antibody to be approved for the treatment of HIV-1 infection. Ibalizumab, in combination with other antiretroviral(s), is indicated in the EU and USA for the treatment of adults with multidrug-resistant HIV-1 infection [8, 9]. This article reviews the clinical efficacy and tolerability of ibalizumab in this population and summarizes its pharmacological properties.

2 Pharmacodynamic Properties of Ibalizumab

Ibalizumab inhibits the entry of HIV-1 into CD4 cells by interfering with the post-attachment steps required for viral entry, thereby preventing viral transmission via cell–cell fusion [8, 9]. Specifically, ibalizumab prevents conformational changes in the gp120-CD4 complex that enable co-receptor binding and fusion [3]. Epitope mapping and structural studies have demonstrated that ibalizumab binds to an epitope in the second domain of the CD4 receptor, on a surface opposite both the gp120 and major histocompatibility complex-class II (MHC-II) binding sites [10-12]. Therefore, ibalizumab does not interfere with MHC-II-mediated immune function [12]. Ibalizumab also prevents HIV-1-induced syncytium formation between infected and uninfected CD4 cells [13].

2.1 Antiviral Activity

The antiviral activity of ibalizumab against HIV-1 is well established in vitro [8, 9]. Ibalizumab inhibited the replication of laboratory strains and clinical isolates of CCR5- and CXCR4-tropic HIV-1 in peripheral blood lymphocytes [8]. In culture, the concentration of ibalizumab at which 50% of viral replication was inhibited (i.e. the effective concentration; EC_{50}) was 0.4–600 (median 8) ng/mL against HIV-1 group M isolates (subtypes A, B, C, D, E or O). Ibalizumab inhibited 17 clinical isolates of subtype B in an infection assay [EC_{50} 8.8–16.9 ng/mL; maximum percent inhibition (MPI) 89–99%]. The drug also inhibited CCR5-tropic (EC_{50} 59–66 ng/mL) and CXCR4-tropic (EC_{50} 44–59 ng/mL) clinical isolates of subtypes B, C and D [8].

Ibalizumab demonstrated breadth and potency against HIV-1 when analyzed against a large ($n = 116$), diverse, clinically relevant panel of pseudoviruses [11]. Ibalizumab achieved 50% inhibition of infection in 92% of viruses and 80% inhibition in 66% of viruses. The median half-maximal inhibitory concentration (IC_{50}) of ibalizumab was 0.03 μg/mL, which was lower than those of the broadly neutralizing monoclonal antibodies PG9 (0.11 μg/mL) and VRC01 (0.22 μg/mL) [11].

The antiviral activity of ibalizumab correlated with complete CD4 cell receptor coating by ibalizumab early in the dosing period [14, 15]. In a phase Ia proof-of-concept study, complete receptor coating lasted for 4–6 days, 8–20 days and 15–34 days following single ibalizumab doses of 3, 10 and 25 mg/kg, respectively [14]. In a phase Ib study, complete receptor coating was observed at serum ibalizumab concentrations of > 5 μg/mL, with partial receptor coating seen at serum concentrations of 0.5–5 μg/mL and receptor uncoating seen at serum concentrations of < 0.5 μg/mL [15]. In the phase III TMB-301 study (Sect. 4.2), the proportion of patients exhibiting ≥ 85% CD4 cell receptor occupancy was 97% on day 21 and 81% at week 25 [16].

When tested in combination with other antiretrovirals, there were no antagonistic effects between ibalizumab and any of the agents tested, including abacavir, atazanavir, didanosine, efavirenz, emtricitabine, enfuvirtide, maraviroc, tenofovir and zidovudine [8]. Ibalizumab exhibited synergistic in vitro antiretroviral activity against HIV-1 when coadministered with enfuvirtide, providing support for the strategy of combining agents which act at sequential steps of the viral entry process [17].

2.2 Resistance

The primary mechanism of resistance to ibalizumab appears to be reduced expression or loss of potential N-linked glycosylation sites (PNGS) in the V5 loop of gp120 [11, 18]. In vitro, the complete absence of a PNGS in the N-terminus of V5 was associated with marked resistance to ibalizumab (median MPI 37%; $p < 0.001$) [11]. Ibalizumab susceptibility was also independently associated with the absence of the PNGS at position 386 ($p = 0.016$) and the side chain length of residue 375 ($p = 0.008$). Ibalizumab exhibited complementary resistance to VRC01 and soluble CD4, which was partly mediated by the V5 PNGS [11]. Loss of V5 PNGS was also associated with reduced susceptibility to ibalizumab in HIV-1 isolates from patients ($n = 14$) participating in a 9-week phase Ib study [18]. The number of V5 PNGS significantly ($p < 0.0001$) correlated with ibalizumab susceptibility. Viral clones with two V5 PNGS were efficiently inhibited by ibalizumab (median MPI 99%), while clones with a single V5 PNGS had reduced susceptibility (median MPI 71%) and clones lacking V5 PNGS were resistant to ibalizumab (median MPI 40%) [18].

Among adults with multidrug-resistant HIV-1 infection who were treated with ibalizumab in the TMB-301 study (Sect. 4.2), seven patients met the criteria for virological failure (i.e. two consecutive measurements after day 14 that showed a reduction from baseline in viral load of < 0.5

$\log_{10}$ copies/mL) and three patients met the criteria for viral rebound (i.e. an increase of ≥ 1.0 $\log_{10}$ copies/mL in viral load from the nadir value) [16]. Nine of these patients demonstrated reduced susceptibility to ibalizumab as determined by lower MPI, which was related to loss of PNGS in eight patients [16].

To date, there are no commercially available resistance testing methods for patients with suspected resistance to ibalizumab [19].

2.3 Cross-Resistance

Phenotypic and genotypic testing demonstrated no evidence of cross-resistance between ibalizumab and any approved antiretroviral agents (e.g. NRTIs, NNRTIs, PIs, INSTIs or entry inhibitors) [8, 9]. In vitro, HIV-1 variants associated with enfuvirtide resistance (namely G36D, V38A and N43D) retained susceptibility to ibalizumab [15]. Similarly, ibalizumab-resistant HIV remained susceptible to enfuvirtide [15].

Ibalizumab was active against HIV-1 strains resistant to currently approved antiretroviral agents [8, 9]. The susceptibility of HIV-1 to ibalizumab was not impacted by baseline resistance to NRTIs, NNRTIs, PIs, INSTIs or entry inhibitors in isolates from patients with multidrug-resistant HIV-1 entering the TMB-301 study (Sect. 4.2) [20]. At study entry, the overall mean ibalizumab MPI was 91% and the overall mean fold change in the concentration of drug required to inhibit 50% of the MPI ($IC_{halfmax}$ fold change) was 1.2. Mean MPI values for ibalizumab were 81, 98, 89 and 91% and mean $IC_{halfmax}$ fold changes were 1.3, 0.9, 1.1 and 1.0 against isolates with wild-type susceptibility to NRTIs, NNRTIs, PIs and INSTIs, respectively. In comparison, mean MPI values were 94, 91, 91 and 92% and mean $IC_{halfmax}$ fold changes were 1.2, 1.2, 1.3 and 1.1 against isolates resistant to all NRTIs, NNRTIs, PIs or INSTIs, respectively. Six patients in TMB-301 had HIV-1 with reduced susceptibility to enfuvirtide. Five of these had MPI values of 84–99% and $IC_{halfmax}$ fold changes of 0.7–1.4, while one had HIV-1 with reduced ibalizumab susceptibility (MPI 41%; $IC_{halfmax}$ fold change 6.2). Ibalizumab had MPI values of 94 and 100% against two isolates with reduced susceptibility to maraviroc [20].

3 Pharmacokinetic Properties of Ibalizumab

Ibalizumab demonstrates non-linear pharmacokinetics following administration of single intravenous doses of 0.3–25 mg/kg [8, 9]. Across a clinically relevant dose range of 800–2000 mg, the maximum serum concentration (C_{max}) of ibalizumab increases dose-proportionally, while increases in the area under the concentration–time curve (AUC) are greater than dose-proportional [9]. Following administration of a single loading dose of 2000 mg followed by a maintenance dose of 800 mg every 2 weeks (i.e. the recommended dosing regimen; Sect. 6), steady-state concentrations of ibalizumab are attained after the first 800 mg maintenance dose [8, 9]. The median time to C_{max} is dose-dependent [9].

The volume of distribution of ibalizumab is ≈ 4.8 L [8, 9]. Clearance decreases and the elimination half-life increases with increasing ibalizumab dose [8]. Following single doses of 10 and 25 mg/kg, the clearance of ibalizumab is 0.5 and 0.36 mL/h/kg and the elimination half-life is 37.8 and 64.1 h [9]. Elimination is dose-dependent and non-linear. Given that ibalizumab is a protein, it is expected to be degraded into small peptides and amino acids [9].

The concentration of ibalizumab decreases with increasing bodyweight; however, this is not likely to impact the virological outcome and no dosage adjustments based on bodyweight are considered necessary [8, 9]. Hepatic and renal impairment are not expected to impact the pharmacokinetics of ibalizumab. While formal drug interaction studies have not been conducted, ibalizumab is not expected to have drug-drug interactions based on its mechanism of action and target-mediated drug disposition [8, 9].

4 Therapeutic Efficacy of Ibalizumab

4.1 Phase II Trials

The potential of ibalizumab for the treatment of multidrug-resistant HIV-1 infection was initially shown in two randomized, double-blind, phase II trials: a 48-week, placebo-controlled, phase IIa trial (TNX-355.03) [21] and a 24-week, phase IIb dose–response trial (TMB-202) [22] (conference abstracts). Of note, these trials used ibalizumab dosages that differed from the subsequently approved regimen (Sect. 6).

In TNX-355.03, patients infected with HIV-1 resistant to three classes of antiretrovirals were randomized to receive ibalizumab 10 mg/kg weekly for 8 weeks followed by 10 mg/kg every 2 weeks ($n = 27$), ibalizumab 15 mg/kg every 2 weeks ($n = 28$), or placebo ($n = 27$); all patients received an OBR [21]. Patients who experienced virological failure (i.e. < 0.5 $\log_{10}$ reduction from baseline in viral load after week 16) were switched to open-label ibalizumab 15 mg/kg every 2 weeks plus a new OBR. The mean change from baseline in viral load at week 24 (primary endpoint) was − 1.16 $\log_{10}$ copies/mL with the ibalizumab 10 mg/kg regimen and − 0.95 $\log_{10}$ copies/mL with ibalizumab 15 mg/kg every 2 weeks versus − 0.20 $\log_{10}$ copies/mL with placebo (both $p < 0.01$) [21]. Results were durable through 48 weeks [23].

In TMB-202, heavily treatment-experienced patients with HIV-1 infection were randomized to receive ibalizumab 800 mg every 2 weeks ($n = 59$) or ibalizumab 2000 mg every 4 weeks ($n = 54$) with all patients also receiving an OBR

[22]. The proportion of patients with a viral load of < 50 copies/mL at week 24 (primary endpoint) was 44% with ibalizumab 800 mg every 2 weeks and 28% with ibalizumab 2000 mg every 4 weeks. The mean reduction from baseline in viral load at week 24 was 1.6 $\log_{10}$ copies/mL in patients receiving ibalizumab 800 mg every 2 weeks and 1.5 $\log_{10}$ copies/mL in patients receiving ibalizumab 2000 mg every 4 weeks. Corresponding mean increases from baseline in CD4+ cell count at week 24 were 37 and 40 cells/μL [22]. Based on the results of TMB-202, the 2000 mg loading dose followed by 800 mg every 2 weeks was subsequently taken forward into the phase III TMB-301 trial (Sect. 4.2) [24].

4.2 Phase III Trials

The therapeutic efficacy of ibalizumab in patients with multidrug-resistant HIV-1 infection was evaluated in a multicentre, open-label, phase III trial (TMB-301) [16]. TMB-301 enrolled 40 adults (aged ≥ 18 years) with multidrug-resistant HIV-1 infection and a viral load of > 1000 copies/mL while receiving ART for ≥ 8 weeks. Patients were required to have received ART for ≥ 6 months, with documented genotypic or phenotypic resistance to at ≥ 1 drug in ≥ 3 drug classes. The trial consisted of a control period (days 0–6), during which patients were monitored while receiving their current ART regimen; a functional monotherapy period (days 7–13), during which patients received an intravenous loading dose of ibalizumab 2000 mg while continuing their previous ART regimen; and a maintenance period (day 14 to week 25), during which patients were initiated on an optimized background regimen (OBR) on day 14 and received intravenous ibalizumab 800 mg every 14 days, starting on day 21. If needed to construct a viable regimen, the OBR could include an investigational antiretroviral agent [16].

At baseline, 50% of patients had HIV-1 infection resistant to all the drugs in ≥ 3 antiretroviral classes and 33% of patients had resistance to all the drugs in four classes; 13% of patients had documented resistance to all approved antiretroviral agents [16]. Patients had received 3–22 (median 10) antiretroviral drugs. The median age of patients was 53 years and most patients were male (85%). The median duration of HIV-1 infection was 23 years (range 2–30 years). The primary endpoint was the proportion of patients with a decrease in viral load of ≥ 0.5 $\log_{10}$ copies/mL from baseline to day 14 (i.e. 7 days after administration of the loading dose) [16].

Ibalizumab demonstrated potent antiviral activity in adults with multidrug-resistant HIV-1 infection [16]. A significantly higher proportion of patients experienced a decrease in viral load of ≥ 0.5 $\log_{10}$ copies/mL during the functional monotherapy period than during the control period (Table 1). There were no clinically meaningful differences in this endpoint across patient subgroups including sex, age (< 50 or ≥ 50 years), race (Caucasian, Asian or other), country of residence (Taiwan or USA) and use of an INSTI or an investigational agent. At the end of the maintenance period (week 25), 50% of patients had achieved a viral load of < 200 copies/mL; 43% had a viral load of < 50 copies/mL. The mean reduction from baseline in viral load was 1.6 $\log_{10}$ copies/mL (Table 1). Among patients with a baseline CD4 + cell count of < 50 cells/μL ($n = 17$), 18 and 24% achieved a viral load of < 50 and 200 copies/mL. Corresponding rates among patients with a baseline CD4+ cell count of ≥ 50 cells/μL ($n = 23$) were 61 and 70% [16].

Seven patients did not achieve a ≥ 0.5 $\log_{10}$ copies/mL reduction in viral load from baseline to the end of the functional monotherapy period [25]. In these patients, the mean decrease in viral load at week 25 was 1.3 $\log_{10}$ copies/mL, compared with 0.1 $\log_{10}$ copies/mL at the end of the

Table 1 Efficacy of ibalizumab in adults with multidrug-resistant HIV-1 infection in study TMB-301 [16]

ITT population ($n = 40$)	End of control period (day 6)	End of functional monotherapy period[a] (day 14)	End of maintenance period[b] (week 25)
	Current ART	IBA + previous ART	IBA + OBR
Decrease in viral load from BL (% pts)			
≥ 0.5 $\log_{10}$ copies/mL	3	83[c]*	63
≥ 1.0 $\log_{10}$ copies/mL	0	60	55
Mean change from BL in viral load ($\log_{10}$ copies/mL)	0.0	− 1.1*	− 1.6
Viral load (% pts)			
< 50 copies/mL			43
< 200 copies/mL			50

ART antiretroviral therapy, *BL* baseline, *IBA* ibalizumab, *ITT* intention-to-treat, *OBR* optimized background regimen, *pts* patients

*$p < 0.001$ vs control period

[a]Pts received an intravenous loading dose of IBA 2000 mg on the first day of the functional monotherapy period (i.e. day 7)

[b]During the maintenance period (day 14 to week 25), pts initiated an OBR on day 14 and received intravenous IBA 800 mg every 14 days, starting on day 21

[c]Primary endpoint

functional monotherapy period. Three patients achieved a viral load of < 50 copies/mL and one achieved a 1.1 $\log_{10}$ copies/mL reduction in viral load by week 25, indicating that virological response may take longer to achieve in some patients with multidrug-resistant HIV-1 infection [25].

At week 25, the mean increase from baseline in CD4+ cell count was 62 cells/μL [16]. This increase was numerically lower in patients with a baseline CD4+ cell count of < 50 cells/μL (17 cells/μL) than in those with a baseline CD4+ cell count of ≥ 50 cells/μL (78 cells/μL), although the difference was not statistically significant [16].

4.3 Expanded Access Protocol

Ibalizumab plus an OBR maintained virological suppression over the longer term (up to 96 weeks) in a multicentre, open-label, phase III expanded access protocol (TMB-311) [26-29]. Patients in TMB-311 included those who had previously received ibalizumab in TMB-202 and TMB-301 (cohort 1) as well as a separate cohort of treatment-experienced patients with no history of ibalizumab treatment who were on a failing regimen (cohort 2) [26].

From TMB-202, 12 patients entered TMB-311 and continued receiving ibalizumab 800 mg every 2 weeks or 2000 mg every 4 weeks under an investigator-sponsored investigational new drug protocol [26]. All patients had a viral load of < 50 copies/mL at the time of the last visit. Ten patients withdrew from the protocol to receive commercially available ibalizumab [26]. Of the 31 patients who completed TMB-301, 27 entered TMB-311, where they continued to receive ibalizumab 800 mg once every 2 weeks for up to 96 weeks [27, 28]. The median reduction from baseline in viral load was 2.5 $\log_{10}$ copies/mL at both week 24 and 48 [27] and 2.8 $\log_{10}$ copies/mL at week 96 [28]. At week 48, 59 and 63% of patients achieved a viral load of < 50 and < 200 copies/mL. All 15 patients with a viral load of < 50 copies/mL at week 24 maintained virological suppression to week 48 [27]. Of these, 14 patients maintained virological suppression through week 96, with one additional patient achieving virological suppression by week 96 [28]. Among the 22 patients who completed 96 weeks of treatment, the median increase in CD4+ cell count at week 96 was 45 cells/μL [28].

Patients in cohort 2 ($n = 38$) started an OBR at the same time as they received their first 2000 mg loading dose of ibalizumab, after which they received ibalizumab 800 mg every 2 weeks [29]. The proportion of patients achieving a ≥ 0.5 $\log_{10}$ copies/mL reduction in viral load on day 7 (primary endpoint) was 76%. The median reduction from baseline in viral load was 2.6 $\log_{10}$ copies/mL at both week 24 and 48. Of the 24 patients who completed 24 weeks of treatment, 11 (46%) had a viral load of < 50 copies/mL at week 24. Three patients withdrew from the expanded access protocol prior to week 24 and a further seven patients withdrew between week 24 and week 48 to receive commercially available ibalizumab. Of the 17 patients who completed 48 weeks of treatment, 8 (47%) had a viral load of < 50 copies/mL at week 48 [29].

4.4 Real-World Setting

Preliminary data from the real-world setting provide supportive evidence for the antiviral efficacy of ibalizumab for the treatment of multidrug-resistant HIV-1 infection. A retrospective, observational pilot study reviewed the medical records of nine patients from seven physician office infusion centres in the USA [30]. Patients had advanced HIV-1 infection and had received intravenous ibalizumab 2000 mg followed by 800 mg every 2 weeks for 4–43 (median 33) weeks. At baseline, 67% of patients were resistant to all drugs in ≥ 1 antiretroviral class, 44% to all drugs in ≥ 2 classes, 33% to all drugs in ≥ 3 classes and 11% to all approved drugs in all classes (NRTIs, NNRTIs, PIs and INSTIs). The median reduction from baseline in viral load was 2.7 $\log_{10}$ copies/mL at 4–10 weeks, 1.6 $\log_{10}$ copies/mL at 14–22 weeks, 0.07 $\log_{10}$ copies/mL at 24–37 weeks and 1.6 $\log_{10}$ copies/mL at 40–58 weeks. The proportion of patients with a decrease in viral load of ≥ 0.5 $\log_{10}$ copies/mL was 75% at 4–10 weeks and 50% at all other timepoints [30].

5 Tolerability of Ibalizumab

Ibalizumab was generally well tolerated in patients with multidrug-resistant HIV-1 infection. In the pivotal phase III trial (TMB-301), the overall incidence of adverse events (AEs) was 80%, most of which were mild in severity [16]. The most commonly reported AEs were diarrhoea, dizziness, fatigue, nausea, pyrexia and rash (Fig. 1). Grade 3 or 4 AEs occurred in 28% of patients and AIDS-defining AEs occurred in 10% of patients. Serious AEs were reported in 23% of patients and 13% of patients discontinued treatment due to AEs. There were four deaths, none of which were considered to be related to ibalizumab [16].

The tolerability profile of ibalizumab in the cohort of ibalizumab-naive patients enrolled in TMB-311 ($n = 38$) was consistent with that seen in TMB-301 [29]. Most AEs were mild to moderate in severity. The most common treatment-emergent AEs (TEAEs) were diarrhoea (24%), headache (21%), cough (16%), fatigue (16%), nausea (16%) and rash (16%). Grade ≥ 3 TEAEs were reported in 24% of patients; two events were fatal but were not considered to be related to ibalizumab [29].

The tolerability of ibalizumab was maintained over the longer-term in TMB-311; no new safety concerns emerged between week 25 and 96 [28].

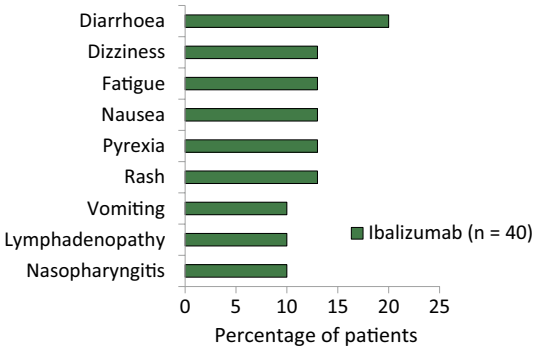

Fig. 1 Most commonly reported (incidence ≥ 10%) adverse events in study TMB-301 [16]

5.1 Adverse Events of Special Interest

Immune reconstitution inflammatory syndrome (IRIS) has been observed in patients receiving combination ART, including ibalizumab [8, 9]. Two of 153 patients treated with ibalizumab in TMB-301 and TMB-202 developed IRIS manifested as an exacerbation of progressive multifocal leukoencephalopathy and of cryptococcal cutaneous infection, respectively; both AEs were serious and resulted in discontinuation of ibalizumab [9]. One patient in TMB-311 also developed IRIS, which was considered to be possibly related to ibalizumab [29]. Evaluation of inflammatory symptoms is recommended, with institution of treatment when necessary [8, 9].

Hypersensitivity reactions to ibalizumab have been observed, including rash [9]. Most rashes occurred within 1–3 weeks of the first dose of ibalizumab, were mild to moderate in severity and resolved within 1–3 weeks with continued ibalizumab administration [9]. One patient in TMB-301 experienced eight episodes of rash, one of which was severe and considered to be related to ibalizumab [16]. If a rash develops, symptomatic therapy (e.g. corticosteroids and/or antihistamines) should be initiated when appropriate and clinical status monitored [9].

As with all therapeutic proteins, ibalizumab has the potential for immunogenicity [8, 9]. Among ibalizumab-treated patients in TMB-301 and TMB-202 ($n = 153$), low-titre anti-drug antibodies (ADAs) were detected in one patient. The emergence of ADAs was not associated with adverse reactions or reduced ibalizumab efficacy in this patient [8, 9].

6 Dosage and Administration of Ibalizumab

Ibalizumab, in combination with other antiretroviral(s), is indicated in the USA for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen [8] and in the EU for the treatment of adults infected with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen [9].

Ibalizumab should be administered as an intravenous infusion by a trained healthcare professional [8, 9]. The recommended dosage of ibalizumab is a single 2000 mg loading dose followed by a maintenance dose of 800 mg once every 2 weeks. The duration of the first infusion (loading dose) should be ≥ 30 min, and patients should be observed during and for 1 h after completion of ibalizumab administration. If no infusion-related adverse reactions are reported, the duration of the subsequent infusions (maintenance doses) can be reduced to ≥ 15 min and the post-infusion observation time can be reduced to 15 min. If a maintenance dose (800 mg) is missed by ≥ 3 days, a loading dose (2000 mg) should be administered as early as possible, with recommencement of maintenance dosing (800 mg) every 2 weeks thereafter [8, 9].

The efficacy and tolerability of ibalizumab in paediatric patients has not been established [8, 9]. There are no adequate data regarding the use of ibalizumab in pregnant women [8, 9]; thus, its use during pregnancy is not recommended [9]. Women receiving ibalizumab should not breastfeed their infants [8, 9]. Local prescribing information should be consulted for detailed information regarding use in special patient populations, drug interactions, contraindications and other warnings and precautions.

7 Current Status of Ibalizumab in Multidrug-Resistant HIV-1 Infection

Although there have been major advances in ART in recent years, HIV drug resistance is an ongoing problem worldwide [31]. Patients with multidrug-resistant HIV-1 infection have limited treatment options. European guidelines for patients with virological failure, resistance mutations and limited treatment options recommend the use of experimental and new drugs, favouring clinical trials (but avoiding functional monotherapy) [2]. Likewise, current US guidelines also recommend enrolling patients with multidrug-resistant HIV-1 infection in a clinical trial of an investigational agent [1]. Therefore, the search for new treatments for these difficult-to-treat patients remains a priority.

While most currently available antiretroviral classes interfere with HIV-1 replication and function after the virus has entered and infected the host cell, HIV-1 entry inhibitors target the vital early stages of the HIV life cycle [32], thereby preventing viral entry into the cell (Sect. 1). Until recently, maraviroc and enfuvirtide were the only entry inhibitors approved for the treatment of HIV-1 infection. Ibalizumab,

an entry inhibitor with a unique mechanism of action, is the first monoclonal antibody to be approved for the treatment of HIV-1 infection. As a post-attachment inhibitor, ibalizumab inhibits the entry of HIV-1 into CD4 cells, thereby preventing co-receptor binding and fusion (Sect. 2). The long half-life of ibalizumab allows for an extended dosing interval (Sect. 3), mitigating its requirement to be administered intravenously. Another advantage of ibalizumab is the low potential for drug-drug interactions (Sect. 3).

The approval of ibalizumab for the treatment of multidrug-resistant HIV-1 infection [8, 9] was based on the results of a phase III trial (TMB-301), in which ibalizumab demonstrated potent antiviral efficacy in adults with multidrug-resistant HIV-1 infection (Sect. 4.2). Most patients achieved a viral load reduction of ≥ 0.5 $\log_{10}$ copies/mL 7 days after ibalizumab was added to a failing antiretroviral regimen. Such a reduction has been shown to predict a decreased risk of clinical progression, and is considered a clinically meaningful endpoint [33]. After 24 weeks of treatment with ibalizumab plus an OBR, almost half of all patients achieved an undetectable viral load (Sect. 4.2), with virological suppression maintained over the longer term (up to 96 weeks) in an expanded access protocol (Sect. 4.3). Data from earlier phase II trials (Sect. 4.1) and preliminary data from the real-world setting (Sect. 4.4) support the phase III findings.

Although limited to a small number of patients, currently available clinical trial data suggest that ibalizumab is generally well tolerated in patients with multidrug-resistant HIV-1 infection (Sect. 5). Most reported AEs were likely to be associated with the patients' advanced HIV/AIDS. AEs related to IRIS, which is commonly associated with combination ART, were observed relatively infrequently (Sect. 5.1).

It should be noted that in addition to its small sample size, the TMB-301 trial has other important limitations, including the absence of a control group for the evaluation of longer-term virological response and the short duration for analysis of secondary and safety endpoints [16]. However, considering the relatively small population of patients with multidrug-resistant HIV-1 infection and the fact that these patients have limited treatment options and a high risk of mortality, the US FDA considered the sample size to be acceptable and the size of the safety database to be adequate [34]. Nevertheless, post-marketing pharmacovigilance data are needed to fully define the safety profile of ibalizumab [16, 34]. Another limitation of TMB-301 is the fact that 43% of patients received an investigational antiretroviral drug as part of their OBR [16], thereby complicating the interpretation of the results.

Monoclonal antibody therapies for rare diseases are often associated with high costs [35]. Indeed, the wholesale annual acquisition cost for ibalizumab is estimated to be US$118,000 [36], without considering the additional cost of the patients' current OBR. A model-based pharmacoeconomic analysis in the USA demonstrated that ibalizumab was not a cost effective treatment option for patients with multidrug-resistant HIV-1 infection [37]. For the estimated 5000 patients with multidrug-resistant HIV-1 infection in the USA, adding ibalizumab to an OBR increased costs by US$708 million over 5 years [37].

In conclusion, although additional studies and long-term post-marketing data are needed to fully determine its efficacy and safety, current evidence indicates that ibalizumab is a valuable option for the treatment of multidrug-resistant HIV-1 infection where limited treatment options are available.

Data Selection Ibalizumab: 194 records identified	
Duplicates removed	79
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	69
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	9
Cited efficacy/tolerability articles	13
Cited articles not efficacy/tolerability	24
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were ibalizumab, Trogarzo, Hu1A8, TMB355, TNX255, HIV-1. Records were limited to those in English language. Searches last updated 6 January 2020	

Acknowledgements During the review process, the manufacturer of ibalizumab was also offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with Ethical Standards

Funding The preparation of this review was not supported by any external funding.

Conflict of interest Hannah Blair is a salaried employee of Adis International Ltd/Springer Nature, is responsible for the article content and declares no relevant conflicts of interest.

References

1. US Department of Health and Human Services. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2019. https://aidsinfo.nih.gov/guidelines. Accessed 6 Jan 2020.
2. European AIDS Clinical Society. Guidelines version 9.1. 2018. https://eacsociety.org. Accessed 6 Jan 2020.

3. Iacob SA, Iacob DG. Ibalizumab targeting CD4 receptors, an emerging molecule in HIV therapy. Front Microbiol. 2017;8:2323.
4. Grover D, Copas A, Green H, et al. What is the risk of mortality following diagnosis of multidrug-resistant HIV-1? J Antimicrob Chemother. 2008;61(3):705–13.
5. Zaccarelli M, Tozzi V, Lorenzini P, et al. Multiple drug class-wide resistance associated with poorer survival after treatment failure in a cohort of HIV-infected patients. AIDS. 2005;19(10):1081–9.
6. Xu F, Acosta EP, Liang L, et al. Current status of the pharmacokinetics and pharmacodynamics of HIV-1 entry inhibitors and HIV therapy. Curr Drug Metab. 2017;18(8):769–81.
7. Henrich TJ, Kuritzkes DR. HIV-1 entry inhibitors: recent development and clinical use. Curr Opin Virol. 2013;3(1):51–7.
8. US FDA. Trogarzo™ (ibalizumab-uiyk) injection, for intravenous use: US prescribing information. 2018. https://www.accessdata.fda.gov. Accessed 6 Jan 2020.
9. European Medicines Agency. Trogarzo (ibalizumab) 200 mg concentrate for solution for infusion: summary of product characteristics. 2019. https://ec.europa.eu. Accessed 6 Jan 2020.
10. Freeman MM, Seaman MS, Rits-Volloch S, et al. Crystal structure of HIV-1 primary receptor CD4 in complex with a potent antiviral antibody. Structure. 2010;18(12):1632–41.
11. Pace CS, Fordyce MW, Franco D, et al. Anti-CD4 monoclonal antibody ibalizumab exhibits breadth and potency against HIV-1, with natural resistance mediated by the loss of a V5 glycan in envelope. J Acquir Immune Defic Syndr. 2013;62(1):1–9.
12. Song R, Franco D, Kao CY, et al. Epitope mapping of ibalizumab, a humanized anti-CD4 monoclonal antibody with anti-HIV-1 activity in infected patients. J Virol. 2010;84(14):6935–42.
13. Reimann KA, Lin W, Bixler S, et al. A humanized form of a CD4-specific monoclonal antibody exhibits decreased antigenicity and prolonged plasma half-life in rhesus monkeys while retaining its unique biological and antiviral properties. AIDS Res Hum Retrovir. 1997;13(11):933–43.
14. Kuritzkes DR, Jacobson J, Powderly WG, et al. Antiretroviral activity of the anti-CD4 monoclonal antibody TNX-355 in patients infected with HIV type 1. J Infect Dis. 2004;189(2):286–91.
15. Jacobson JM, Kuritzkes DR, Godofsky E, et al. Safety, pharmacokinetics, and antiretroviral activity of multiple doses of ibalizumab (formerly TNX-355), an anti-CD4 monoclonal antibody, in human immunodeficiency virus type 1-infected adults. Antimicrob Agents Chemother. 2009;53(2):450–7.
16. Emu B, Fessel J, Schrader S, et al. Phase 3 study of ibalizumab for multidrug-resistant HIV-1. N Engl J Med. 2018;379(7):645–54.
17. Zhang XQ, Sorensen M, Fung M, et al. Synergistic in vitro antiretroviral activity of a humanized monoclonal anti-CD4 antibody (TNX-355) and enfuvirtide (T-20). Antimicrob Agents Chemother. 2006;50(6):2231–3.
18. Toma J, Weinheimer SP, Stawiski E, et al. Loss of asparagine-linked glycosylation sites in variable region 5 of human immunodeficiency virus type 1 envelope is associated with resistance to CD4 antibody ibalizumab. J Virol. 2011;85(8):3872–80.
19. Beccari MV, Mogle BT, Sidman EF, et al. Ibalizumab, a novel monoclonal antibody for the management of multidrug-resistant HIV-1 infection. Antimicrob Agents Chemother. 2019;63(6):e00110–e119.
20. Weinheimer S, Cohen Z, Marsolais C, et al. Ibalizumab susceptibility in patient HIV isolates resistant to antiretrovirals [abstract no. 561 plus poster]. In: 25th Conference on Retroviruses and Opportunistic Infections. 2018.
21. Norris D, Morales J, Gathe J, et al. Phase 2 efficacy and safety of the novel entry inhibitor, TNX-355, in combination with optimized background regimen [abstract no. TUPE0058]. In: 16th International AIDS Conference. 2006.
22. Khanlou H, Gathe JJ, Schrader S, et al. Safety, efficacy, and pharmacokinetics of ibalizumab in treatment-experienced HIV-1 infected patients: a phase 2b study [abstract no. H2-794b]. In: 51st Interscience Conference on Antimicrobial Agents and Chemotherapy. 2011.
23. Norris D, Morales J, Godofsky E, et al. TNX-355, in combination with optimized background regimen (OBR), achieves statistically significant viral load reduction and CD4 cell count increase when compared with OBR alone in phase 2 study at 48 weeks [abstract no. THLB0218]. In: 16th International AIDS Conference. 2006.
24. European Medicines Agency. Trogarzo (ibalizumab) assessment report. 2019. https://ema.europa.eu. Accessed 6 Jan 2020.
25. DeJesus E, Emu B, Weinheimer S, et al. Outcomes of patients not achieving primary endpoint from an ibalizumab phase III trial [abstract no. P064]. J Int AIDS Soc. 2018;21(Suppl 8):55–6.
26. Moyle G, Perno CF, Emu B, et al. Long-term efficacy, safety and durability of ibaliumab in expanded access study [abstract no. PE13/16 plus poster]. HIV Med. 2019;20(Suppl 9):169.
27. Emu B, Fessel WJ, Schrader S, et al. Forty-eight-week safety and efficacy on-treatment analysis of ibalizumab in patients with multi-drug resistant HIV-1 [abstract no. 1686]. Open Forum Infect Dis. 2017;4(Suppl 1):38–9.
28. Emu B, Lalezari J, Kumar P, et al. Ibalizumab: 96-week data and efficacy in patients resistant to common antiretrovirals [abstract no. 485]. In: 26th Conference on Retroviruses and Opportunistic Infections. 2019.
29. Emu B, DeJesus E, Berhe M, et al. Ibalizumab efficacy and safety through 48 weeks of treatment: results of an expanded access protocol (TMB-311) [abstract no. 661 plus poster]. In: ID week. 2019.
30. Prokesch RC, Schroeder CP, Hardin TC, et al. Real-world use of ibalizumab in physician office infusion centers (POICs) [abstract no. 2494 plus poster]. In: ID week. 2019.
31. World Health Organization. HIV drug resistance report. 2019. https://www.who.int. Accessed 6 Jan 2020.
32. US Department of Health and Human Services. Understanding HIV/AIDS: the HIV life cycle. 2019. https://aidsinfo.nih.gov. Accessed 6 Jan 2020.
33. Murray JS, Elashoff MR, Iacono-Connors LC, et al. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. AIDS. 1999;13(7):797–804.
34. Sheikh V, Murray JS, Sherwat A. Ibalizumab in multidrug-resistant HIV - accepting uncertainty. N Engl J Med. 2018;379(7):605–7.
35. Park T, Griggs SK, Suh DC. Cost effectiveness of monoclonal antibody therapy for rare diseases: a systematic review. BioDrugs. 2015;29(4):259–74.
36. Morrow T. Multidrug resistant HIV drug lauded, but clinical foundation not very deep. Manag Care. 2018;27(6):31–3.
37. Millham L, Scott J, Sax P, et al. Clinical and economic impact of ibalizumab for patients with multidrug-resistant HIV in the United States [abstract no. MOPEB275]. In: 10th International AIDS Society Conference on HIV Science. 2019.