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Ibalizumab: an anti-CD4 monoclonal antibody for the treatment of HIV-1 infection

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The majority of currently available agents for the treatment of HIV-1 infection act by targeting one of several intracellular steps in the viral life cycle. Despite improvements in efficacy and tolerability, the development of viral resistance to these agents is common and significant toxicity and adherence issues still occur. For this reason the development of safe, well tolerated antiviral agents that target a novel step in the viral life cycle remains important. Viral entry into host cells affords several potential extracellular targets for antiretroviral therapy. Ibalizumab, a humanized monoclonal antibody to CD4, the primary host cellular receptor for HIV-1 entry, has been shown to block HIV-1 entry *in vitro*. Early clinical trials have demonstrated significant antiviral efficacy with a >1 $\log_{10}$ reduction in viral load when given as monotherapy. Its long half-life, which allows weekly dosing, and its administration as an intravenous infusion differentiate it from other currently available antiretroviral agents. These properties may prove useful in allowing improved drug delivery to patients who have had difficulty adhering to daily oral regimens. Its unique mode of action reduces the risk of cross-resistance with currently available antiretroviral agents, with the potential to expand the choices available to treat drug-resistant HIV-1.

Keywords: antiretroviral therapy, antiviral, retroviruses

Introduction

The treatment of HIV-1 infection with combination antiretroviral therapy (ART) has significantly decreased HIV-1-related mortality.[1] Successive generations of ART agents have shown improved efficacy and tolerability while minimizing drug-related toxicities. Despite these successes, the ability of HIV-1 to develop resistance and the inability of some patients to adhere to currently available regimens make the continued development of new ART agents important. Therapeutics that target a novel step in the viral life cycle are of particular interest because empirical resistance is unlikely. HIV-1 entry into host cells is a multistep process that offers several potential targets for antiviral therapy.[2] Ibalizumab (formerly TNX-355 and Hu5A8), an anti-CD4 monoclonal antibody that interferes with viral entry, has displayed promising results in early clinical trials.[3,4] Its administration as an intravenous infusion and its pharmacokinetics, which allow weekly dosing, differentiate it from current ART options. This review summarizes the available clinical data on ibalizumab.

Structure/mechanism of action

The process of HIV-1 entry into target cells is initiated when the surface subunit of the HIV-1 envelope glycoprotein (gp120) binds to a cellular CD4 receptor. The resulting conformational changes to the CD4/gp120 complex allow gp120 to bind to a second cellular receptor, chemokine receptor-5 (CCR5) or CX chemokine receptor-4 (CXCR4). This co-receptor binding allows the gp41 molecule of the viral envelope to insert into the target cell membrane, ultimately leading to fusion of the viral envelope and cellular membrane.[2,5,6]

Ibalizumab is a humanized monoclonal antibody of murine origin. Initially reported to bind to an epitope on domain 2 of the extracellular region of CD4, more recent work suggests binding to the interface between domain 1 and domain 2 of CD4, away from the binding site for major histocompatibility complex (MHC) class II molecules.[7,8] It does not inhibit gp120 binding to CD4, which occurs in the domain 1 region. Instead, ibalizumab appears to exert its antiviral effect by post-binding conformational effects that prevent CD4-bound gp120 from interacting with CCR5 or CXCR4.[7,9–12] Other monoclonal antibodies that target domain 1 of CD4 and competitively inhibit gp120 binding have been found to be immunosuppressive due to their interference with MHC class II immune function.[13,14] As of yet, no immunosuppressive effect has been seen with ibalizumab in human trials. Pre-clinical trials in non-human primates showed ibalizumab to be safe and well tolerated.[15]

Human studies

The reported human experience with ibalizumab consists of three clinical trials involving a total of 134 subjects.[3,4,16] The

safety and antiviral efficacy of ibalizumab in humans was first demonstrated in a Phase I study involving 30 HIV-1 positive patients not on ART or on a failing regimen with a plasma HIV-1 RNA level >5000 copies/mL.[4] Subjects received single-dose infusions of ibalizumab over six dose levels ranging from 0.3 to 25 mg/kg. Minimal antiviral efficacy was seen at the 0.3 and 1.0 mg/kg doses. However, dose-related reductions in HIV-1 RNA levels were seen in the three higher dose cohorts, with peak median reductions of viral load of 0.56 $\log_{10}$ in the 3.0 mg/kg dose cohort, 1.33 $\log_{10}$ in the 10 mg/kg cohort and 1.11 $\log_{10}$ in the 25 mg/kg cohort. Peak mean reductions in viral load occurred later in the higher dose cohorts, occurring on day 14 in the 10 mg/kg cohort and day 21 in the 25 mg/kg cohort. The extent and duration of viral suppression correlated with the degree of CD4 cell coating by ibalizumab. Coating was maintained longer in the higher dose cohorts, with a duration of 15–34 days in the 25 mg/kg cohort. Peak increases in CD4 counts ranged from 23 cells/mm^3 in the 0.3 mg/kg dose cohort to 244 cells/mm^3 in the 25 mg/kg dose cohort. Interestingly, these increases peaked at 1 day after infusion, well before the peak declines in viral load, suggesting that the increase may have been due to redistribution of CD4 cells from lymphoid tissue rather than regeneration of CD4 cells in the setting of viral suppression. No antibodies to ibalizumab were detected as late as day 90 after infusion. There were no significant infusion reactions. Adverse events (AEs) that occurred in three or more subjects included headache (13%) and rash (10%). However, these did not result in discontinuation of the infusion in any of the subjects.

A Phase Ib multidose study demonstrated continued safety over an extended treatment period and provided data on the development of ibalizumab resistance.[3] Twenty-two HIV-1-infected subjects off ART or on a stable failing regimen were given ibalizumab at one of three dosing regimens (10 mg/kg weekly, 10 mg/kg loading dose followed by 6 mg/kg every 2 weeks, or 25 mg/kg every 2 weeks) for a 9 week period. Doses were administered by intravenous infusion over ~1 h. All three dosing cohorts exhibited rapid reduction in mean viral load of 0.83–0.96 $\log_{10}$ copies/mL, which peaked in the first to second week of infusion. A viral load reduction of >1.0 $\log_{10}$ was seen in 64% of all subjects across all treatment arms and 20 of 22 subjects experienced a >0.5 $\log_{10}$ reduction. These reductions were transient in all three groups, which returned to baseline viral load by the end of the study period despite evidence of continuing partial or complete coating of CD4 receptors. Resistance testing performed at week 9 showed reduced susceptibility relative to baseline in 13 of 14 samples tested. Resistant isolates remained dependent on CD4 for viral entry, suggesting that resistance did not develop through the use of alternative receptors. Genotypic analysis was unable to identify mutations diagnostic of ibalizumab resistance. Consistent with the allosteric mechanism of ibalizumab's anti-HIV-1 effect, the development of resistance is associated with a reduction in the maximum percentage inhibition rather than the shift in the IC_{50} characteristic of competitive inhibitors.

Earlier *in vitro* data demonstrated synergistic antiviral activity when ibalizumab and the entry inhibitor enfuvirtide were used in combination.[17] Cross-resistance between enfuvirtide and ibalizumab was investigated in the Phase Ib clinical study. Enfuvirtide susceptibility was unchanged in a week 9 isolate with reduced susceptibility to ibalizumab, and enfuvirtide-resistant isolates showed no decrease in susceptibility to ibalizumab, suggesting no cross-resistance between these entry inhibitors.

Ibalizumab was well tolerated, with low numbers of mild to moderate AEs, headache being the only drug-related AE occurring in more than one patient ($n=4$). No subjects were removed from the study due to AEs. In contrast to the prior single-dose study, low levels of anti-ibalizumab antibodies were observed in some subjects. However, they were not associated with lower ibalizumab serum levels, AEs or decreased antiviral effect.

The half-life of immunoglobulin G under normal physiological circumstances is 2–3 weeks.[18] In contrast, the average half-life of ibalizumab is 3–3.5 days.[3] This is consistent with observations of other anti-CD4 antibodies, in which internalization or shedding of the receptor results in more rapid antibody degradation. Increasing trough levels in the two higher dosing regimens suggest this mechanism of elimination is a saturable process.

The 24 week analysis of a randomized, double-blind, placebo-controlled, Phase IIa study has been presented (Table 1).[16] Eighty-two triple class experienced subjects were randomized to receive ibalizumab (10 mg/kg weekly for 8 weeks followed by either 10 mg/kg every 2 weeks or 15 mg/kg every 2 weeks) versus placebo in addition to an optimized background regimen. The primary endpoint of mean change in viral load from baseline at week 24 was evaluated in a modified intention-to-treat population (subjects that had received at least one infusion). Viral load reductions were significantly greater in the two treatment arms, with a mean 0.95 $\log_{10}$

Table 1. Antiviral effects of ibalizumab in combination with an optimized background regimen

Effect	Ibalizumab dose[a] (*N*)		Placebo + OBR (27)
	15 mg/kg + OBR (28)	10 mg/kg + OBR (27)	
Mean change in HIV-1 VL from baseline, $\log_{10}$ copies/mL.	−0.95[b]	−1.16[c]	−0.20
Subjects with ≥1 $\log_{10}$ copies/mL decrease in HIV-1 RNA level, *n* (%)	10 (36)	12 (44)	6 (22)
Subjects with ≥0.5 $\log_{10}$ copies/mL decrease in HIV-1 RNA level, *n* (%)	14 (50)[d]	15 (56)[e]	6 (22)
Subjects with <400 HIV-1 RNA copies/mL, *n* (%)	2 (7)	6 (22)[f]	0 (0)

OBR, optimized background regimen; VL, viral load.
[a]Both treatment arms received 10 mg/kg ibalizumab weekly for 8 weeks followed by either 10 mg/kg or 15 mg/kg every 2 weeks to complete 24 weeks.
P values are in comparison with the placebo group: [b]$P=0.003$; [c]$P<0.001$; [d]$P=0.05$; [e]$P=0.024$; [f]$P=0.02$.

drop in the 15 mg/kg arm and 1.16 in the 10 mg/kg arm compared with 0.20 in the placebo arm.

After the completion of the Phase IIa study, Genentech Inc. acquired Tanox Inc., the sponsor of the above clinical studies of ibalizumab, but ultimately out-licensed ibalizumab to TaiMed Biologics Inc. After some delay as a result of these transactions, TaiMed initiated a 24 week Phase IIb dose-comparison protocol that is still in progress.

Conclusions

Ibalizumab is an anti-CD4 monoclonal antibody that has displayed promising antiviral activity and safety in early clinical trials. Its novel mechanism of action allows antiviral activity regardless of chemokine receptor tropism and suggests that cross-resistance with other classes of antiretrovirals is unlikely. The successful development of ibalizumab would expand the treatment options for patients with drug-resistant strains of HIV-1. Its pharmacokinetics allow an extended dosing interval. This property may allow more convenient self-administration of ART and ensure delivery of drug to patients with poor adherence to daily oral regimens and in resource-poor settings. In addition, long-acting parenteral therapy, by providing immediate, prolonged antiretroviral activity, could play a role in 'seek, test and treat' programmes, rapidly reducing the risk of spread of infection from persons identified. Larger studies of ibalizumab given as part of multidrug regimens are needed.

Transparency declarations

None to declare.

Author contributions

C. J. B. and J. M. J. contributed to writing the manuscript.

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