LFB-R603: a therapeutic CD20 antibody mediates a superior antitumor efficacy in Non-Hodgkin lymphoma xenograft model and B-cell depletion in cynomolgus monkeys


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BACKGROUND: LFB-R603 is an anti-CD20 antibody, characterized by a specific glycosylation pattern containing a high percentage of non fucoylated antibodies molecules at the Fc site. This pattern of glycosylation increases the affinity of antibodies for human FcRn resulting in an increased antibody dependent cell-mediated cytotoxicity (ADCC) by human FcRn-expressing effector cells (1, 2). This antibody is currently in Phase I clinical trial in B-CLL patients and its use may be expanded to other lymphoproliferative diseases such as Non-Hodgkin lymphoma (NHL).

AIMS: The main objective was to study the antitumor efficacy of LFB-R603 in comparison with rituximab in a model of human follicular NHL grown as a xenotransplant in mice. In addition this study aimed to compare the ability of LFB-R603 and rituximab to deplete normal B cells in cynomolgus monkeys.

METHODS: RL cells, derived from a patient with transformed NHL were implanted subcutaneously in SCID mice (3). When tumors became palpable mice were randomized to receive LFB-R603 (4 weekly intravenous injections at dose levels of 10, 30 and 100 mg/kg) and 2 doses for Rituximab (RTX) (30 and 100 mg/kg). Treatment started 13 days after cell injection when tumors became palpable in SCID mice (treatments are indicated by black arrows). LFB-R603 tested at three doses (10, 30 and 100 mg/kg) displayed dose-related efficacy in terms of tumor volume against RL xenografts. Comparison of LFB-R603 and Rituximab showed similar efficacy of both antibodies at the 30 mg/kg dose (p=0.92) but a significantly stronger activity of LFB-R603 at the 100 mg/kg dose (p<0.001 from day 45 onward).

RESULTS:

I. LFB-R603 mediates superior efficacy than Rituximab in subcutaneous human RL NHL xenografts in SCID mice

Fig. 1. Antibodies were given intravenously once weekly for 4 weeks at 3 doses for LFB-R603 (10, 30 and 100 mg/kg) and 2 doses for Rituximab (RTX) (30 and 100 mg/kg). Treatment started 13 days after cell injection when tumors became palpable in SCID mice (treatments are indicated by black arrows).

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II. LFB-R603 displayed additive antitumor effect with cyclophosphamide in subcutaneous human RL NHL xenografts in SCID mice

Fig. 2. LFB-R603 or Rituximab (RTX) were administered at 60 mg/kg once weekly during 4 weeks, either as single agents or in combination with Cyclophosphamide (CTX) at 50 mg/kg. Treatment was initiated 14 days after RL cell transplantation when tumors were established. Antibodies and vehicle were given intravenously once weekly. Cyclophosphamide was administered intraperitoneally on the same day as the antibody (treatments are indicated by black arrows).

All the doses of 60 mg/kg LFB-R603 displayed greater antitumor efficacy than Rituximab. Furthermore LFB-R603 exhibited an additive antitumor effect with Cyclophosphamide. An additive effect of cyclophosphamide and rituximab was also observed.

III. LFB-R603 shows a higher B-cell depletion in Cynomolgus monkeys than Rituximab

Fig. 3. Profile of depletion of circulating B lymphocytes induced by repeated intravenous administration of different doses of LFB-R603 or Rituximab (RTX) in the cynomolgus monkey (M. fascicularis, 1 animal). Different total doses of antibody were tested: 0.3, 0.9, 3.0, 9.0, 30.0, 0.3 and 0.01 mg/kg for LFB-R603 and 1.5, 0.6, 0.3, 0.2 and 0.06 mg/kg for Rituximab. The administration schedule was one intravenous injection per day for 4 consecutive days.

The different antibody doses administered induced different B-cell depletion percentages. Based on these values, we drew a dose-effect curve and estimated the dose of each antibody that would allow for 50% depletion of the circulating B-cells. The depletion values used were those measured on day 6, the first measurement performed after the 4 injections.

Dose-dependent B-cell depletion was observed in peripheral blood for both antibodies. However, the total dose required for 50% depletion calculated from the dose-effect curve showed that LFB-R603 activity was almost 6 times higher than that of rituximab.

IV. LFB-R603 induces B-cell depletion both in blood and B-cell containing organs/tissues in cynomolgus monkeys

Fig. 4. During a toxicological study, cynomolgus monkeys were exposed to a single injection of 0.3, 10 or 100 mg/kg of LFB-R603. B-cell depletion was evaluated in the peripheral blood (A) and in lymphoid tissues (spleen, bone marrow and lymph node) (B). The data represent the mean ± SEM of 4 (control, i.e. 0 mg/kg) or 6 animals (LFB-R603-treated) per group. In peripheral blood B cell depletion was expressed as a percentage of the baseline.

A) B-cell depletion was observed in all monkeys, with >95% peripheral B-cell depletion following the administration of LFB-R603. For the lower tested dose, B-cell depletion was complete at least for 7 days and a slow recovery was observed thereafter in the peripheral blood. In the group of animals treated with the high dose (100 mg/kg), LFB-R603, recovery of B-cells became apparent 77 days after the dose and reached approximately 16% of pre-treatment values on day 113 after-treatment (data not shown).

B) On day 15 after treatment, B-cell depletion in lymphatic tissue (axillary lymph nodes, femoral bone marrow and spleen) was evaluated for all tested doses. Marked dose-dependent reduction was observed. For the higher tested dose, B-cell depletion was also determined during the recovery period i.e. on day 113 post-treatment showing the reconstitution of B-cell population in lymphatic tissue (axillary group).

SUMMARY AND CONCLUSION:

- Compared to Rituximab LFB-R603 showed a superior efficacy in a NHL xenograft model and in B-cell depletion studies performed in cynomolgus monkeys.

- LFB-R603 showed an antitumor additive effect with cyclophosphamide.

- These results suggest that LFB-R603 possesses anti-NHL activity in vivo, can be combined with cyclophosphamide and may be superior to Rituximab.