Efficacy, Safety and Immunogenecity study of Intravenous Infusion of Rituximab (Hetero) and Reference Medicinal Product (Rituximab, Roche) in Indian Patients of Follicular Lymphoma Preliminary report (HERILY)

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Abstract
Objective: To compare the antitumor efficacy, safety, and pharmacodynamics (PD) characteristics of Hetero-Rituximab (test) with Reference Medicinal Product (Rituximab, Roche) in Non-Hodgkin’s Lymphoma (NHL)

Patients and Methods: Total 40 Follicular Lymphoma (FL) patients were randomized to receive intravenous infusion of either test or reference product. Efficacy (best overall response [BOR] rate [primary end point]), safety, PD (CD19), and immunological assessments (secondary end points) were done at the end of cycle 3 and cycle 6.

Results: Out of 40 patients randomized, 17 were in test arm while 23 were in reference arm.

At the end of 6 cycles, BOR (complete response [CR] and partial response [PR]) rate was 64.71% (n=11) in Hetero Rituximab compared to the 43.48% (n=10) in reference arm.

The difference between test and reference proportions of best overall response rate at cycle 6, lies within the pre-specified limit for non-inferiority. Anti-Rituximab antibodies were found to be negative at cycle 3 and cycle 6 for all FL patients. The FL patients who were treated with Hetero Rituximab, showed significant depletion in CD19+ cell which was comparable with Reference drug. Safety and Immunogenic potential of the test drug was comparable to the reference drug in the patients of FL.

Conclusion: Best overall response rate at Cycle 3, Cycle 6 and end of the study lies within the pre-specified limit for non-inferiority which concludes that test product is therapeutically non-inferior to reference medicinal product.

Editorial Viewpoint
• Biosimilars are being introduced into Indian market at a rapid pace.
• In this study establishes non-inferiority of a new rituximab biosimilar in the management of follicular lymphoma.

Introduction
Non-Hodgkin’s lymphoma (NHL) are classified as a heterogeneous group of malignancies arising from lymphoid tissue that are highly responsive to initial therapy but relapse with less responsive disease, accounting for ~5.1% of all cancer cases and 2.7% of all cancer deaths. Its incidence has been increasing over the past several decades globally in North America, Western Europe at an annual rate of 4%. In India as well, reported incidence was on the upsurge at 5.1 per 100,000.3

NHL treatment has dramatically changed with the introduction of rituximab (Rituxan, Genetech, San Francisco, CA). Its greatest impact has been in follicular lymphoma (FL), which constitutes approximately 70% of indolent lymphomas and up to 25% of all cases of NHL. Although there are

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no defined first line therapies for NHL, rituximab has become a standard component in treatment of FL.

Rituximab is the first genetically engineered chimeric (murine-human) monoclonal antibody (mAb) against the CD20 antigen for the treatment of cancer recommended at dosage of 375 mg/m²/infusion, weekly for 4 weeks. Because of its human component, rituximab has low immunogenicity. For approval by the US Food and Drug Administration, multiple studies were conducted internationally. In phase-II Study, low-grade or follicular B-cell non-Hodgkin’s lymphoma patients treated with Rituximab (375 mg/m² per dose) along with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy showed overall response rate of 95%. Most frequent events to rituximab were fever and chills, observed primarily with the first infusion, which conclude additive therapeutic benefit for the combination with no added toxicity.

In phase III study, patients with advanced-stage follicular lymphoma (n=428) were randomly assigned to either CHOP alone arm (n = 205) or CHOP combined with rituximab (R-CHOP) (n = 223). The objective response rate (ORR) was found to be higher (96%) in the group received CHOP plus Rituximab vs 90% in the group received CHOP alone.

Rituximab was approved by the Food and Drug Administration on November 26, 1997 (and by the European Union on June 2, 1998), for the indication of follicular non-Hodgkin’s lymphoma. In 2014, a subcutaneous formulation of Rituxan was further approved by European Commission (EC) for the treatment of both FL and Diffuse Large B-Cell Lymphoma (DLBCL).

Since, rituximab binds to CD20 antigen, its presence in blood samples can interfere with assay of CD20 cells. Hence, rituximab administration can confound CD20 assay measurements. Moreover, CD19 expression mirrors CD20 expression and can therefore serve as a surrogate marker in patients with circulating rituximab.

In India, safety of biosimilar rituximab is already established in Indian patients with two Biosimilar products readily available in market. As per the Guidelines of the Central Drugs Standard Control Organization, comparative clinical trials are critical to demonstrate the similarity in efficacy and safety profiles between the similar biologic and reference biologic. Hence, phase 3, randomized non-inferiority trial was conducted in FL patients to compare the efficacy, safety and immunogenicity of intravenous infusion of test and reference medicinal product.

Material and Methods

This was a phase 3, randomized, multiple-dose, multicentre, comparative, parallel study to evaluate the efficacy, safety of intravenous infusion of rituximab, test and reference medicinal product in previously untreated Indian patients with non-hodgkin’s lymphoma (stage III-IV follicular lymphoma subtype). The study was carried out from Sep 2013 to Aug 2015 at 36 oncology sites of India. The study protocol was approved by office of Drug Controller General of India and Ethics Committees. Independent ethics committees or institutional review boards at participating sites approved the protocol. The study was registered to clinical trial registry-India (CTRI) prior to initiation of the study (CTRI Registration No: CTRI/2013/08/003921). The study was conducted in accordance with the Declaration of Helsinki (2000) and the International Conference on Harmonisation Guidelines for Good Clinical Practice. Written informed consent was obtained from patients or their legally authorised representatives before initiation of any trial procedures.

Key inclusion criteria were male or female ≥18 years and ≤65 years of age (both inclusive), histologically confirmed CD20-positive, previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy, patients who are eligible for rituximab and CHOP, patients with at least one measurable lesion as per International Working Group Response (IWGR) criteria for malignant lymphoma, adequate liver, renal, cardiac and haematological function, subjects with a performance status of 0 to 2 according to the Eastern Cooperative Oncology Group (ECOG), life expectancy more than six months.

Study Treatments

Hetero-Rituximab (Test drug) or reference medicinal product (Reference drug manufactured by Roche) 375 mg/m² was administered on Day 1 of each chemotherapy cycle in combination with CHOP for 6 cycles. Premedication consisting of an anti-pyretic and an antihistaminic, e.g., paracetamol and diphenhydramine or prednisolone or as per institutional standard was administered before each infusion of IMP. Since, this was a parallel open label study, thus no blinding was done.

Endpoints Assessment

Primary efficacy end point of the study was calculated on best overall response rate at the end of cycle 3 and cycle 6. BOR was defined as patients with response of complete response (CR) and partial response (PR). The secondary evaluation was based on evaluation of safety, immunogenicity and clinical pharmacodynamics (PD). Safety was measured by adverse events by monitoring of significant clinical signs and symptoms and laboratory abnormalities during treatment. Immunogenicity was evaluated by assessing blood serum for the presence of anti-rituximab antibodies in all patients at the end.
of cycle 3 and at the end of cycle 6. Clinical Pharmacodynamics was evaluated by circulating B-cell measurements using CD19+ as a surrogate marker for B-cells expressing CD20 at the end of cycle 3 and at the end of cycle 6.

Statistical Analyses

A total of 40 patients were randomized to receive intravenous infusion of either Hetero-Rituximab or reference medicinal product (Rituximab, Roche). During the study, as per randomization schedule, 17 patients received test product and 23 patients received reference medicinal product.

Randomization schedule was generated using SAS version 9.3 before the commencement of the study. Block randomization of size two in ratio of 1:1 (Test: Reference) was generated and balanced treatment allocation within block was ensured at the time of randomization generation. To evaluate safety, a set was made for all patients who received at least one dose of study drug. All statistical analysis was performed using SAS® Version 9.3 (SAS Institute Inc., USA).

Results

Pharmacodynamics and Immunogenicity

Immunogenicity was evaluated by assessing serum for the presence of anti-rituximab antibodies in all patients at baseline, at the end of 3rd cycle and at the end of cycle 6. Anti Rituximab Antibodies were found to be negative at cycle 3 and cycle 6 for all patients. For CD19+ parameter, the Geometric Mean Titer (GMT) was comparable at baseline [FL: Test = 5.08 micro liter (i.e. 2.31%) and Reference = 5.46 micro liter (i.e. 2.45%)] and got reduced over the study period with [FL: Test = 3.36 micro liter (i.e. 1.12%) and Reference = 2.59 micro liter (i.e. 0.96%)] at the end of cycle 6.

Efficacy

A total of 40 FL patients were included for efficacy analysis. As part of the primary efficacy analysis, data was evaluated at the end of cycle 6. At the end of the cycle 6, 17 patients in test arm and 23 patients in Reference arm were evaluable. The result of the study indicates that proportion of patients with best overall response rate (CR + PR) is 64.71% (n=11) in Hetero Rituximab compared to the 43.48% (n=10) in reference Rituximab at the end of the cycle 6. These results shows that the lower limit of 97.06% CI (-12.60%, 55.05%) (Table 1) for the difference between test and reference proportions of best overall response rate at cycle 6, lies within the pre-specified limit for non-inferiority i.e. lower limit > -20% (Table 2).

Additionally, the CR rate was 17.65% (n=03) in patients receiving Hetero Rituximab compared to 13.04% (n=03) patients received reference Rituximab while PR rates were 47.06% (n=08) and 30.43% (n=07) for FL patients who were exposed to test and reference formulations, respectively (refer to Table 14.2.1.1-FL).

Safety Results

A total of 277 adverse events (AEs) were reported by 34 patients during the conduct of study. Of the 277 adverse events, 113 AEs were mild, 134 AEs were moderate and 30 AEs were severe in nature as per common terminology criteria for adverse events (CTCAE) gradation.

The relationship was judged as unlikely for one hundred and two (102) AEs, as possible for one hundred and two (102) AEs, as probable/likely for fifty five (55) AEs and as certain for eighteen (18) AEs.

One hundred sixty nine (169) treatment emergent adverse events (TEAEs) were reported after receipt of Reference Medicinal Product and one hundred and eight (108) TEAEs were reported after receipt of Test Product. One Hundred and Eight TEAEs were reported by 76.47% (n=13) of 17 patients under Test Product, 169 TEAEs were reported by 91.30% (n=21) of 23 patients under Reference Medicinal Product. The outcomes of the TEAEs were 247 AEs – complete recovery, 16 AEs – Ongoing, 10 AEs - Recovered with sequelae, 02 AEs – Unknown, 01 AE – Death and 01 AE – Event worsened.

One (01) death and nine (09) other serious adverse events were reported during the conduct of study. The causality assessment

Table 1: Point estimate and confidence interval for difference in percentage of patients with best overall response rate (ITT;FL Group)

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Difference between proportions (%)</th>
<th>97.06% confidence interval</th>
<th>Acceptance range (%)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 3</td>
<td>11.11%</td>
<td>(-11.71%, 33.93%)</td>
<td>Lower Non-Inferior Limit &gt; -20%</td>
<td></td>
</tr>
<tr>
<td>Cycle 6</td>
<td>21.23%</td>
<td>(-12.60%, 55.05%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of study</td>
<td>5.63%</td>
<td>(-18.58%, 29.83%)</td>
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</tr>
</tbody>
</table>

Table 2: Summary statistics of best overall response rate by treatment group (ITT, FL group)

<table>
<thead>
<tr>
<th>Cycle (No. of patients)</th>
<th>Endpoint</th>
<th>Test product</th>
<th>Reference product</th>
<th>Difference between proportions (Test-reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle: 3 (Test (10): Reference (9))</td>
<td>ORR 100%</td>
<td>88.89%</td>
<td>11.11%</td>
<td></td>
</tr>
<tr>
<td>Cycle: 6 (Test (17): Reference (23))</td>
<td>ORR 64.71%</td>
<td>43.48%</td>
<td>21.23%</td>
<td></td>
</tr>
<tr>
<td>End of study (Test (17): Reference (23))</td>
<td>BOR 88.24%</td>
<td>82.61%</td>
<td>5.63%</td>
<td></td>
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</table>
included 05 serious adverse events (SAEs) (including one death) unlikely related to the study drug (03 SAEs under reference arm and 02 SAEs under test arm) and 05 SAEs as possible (05 SAEs under reference arm). The outcomes of 10 SAEs were 01 - death, 08 - complete recovery and 01 - Recovered with sequelae.

Majority of the patients did not have any clinically significant abnormalities during laboratory assessments, vital recordings etc. However, results which were clinically significant were recorded as adverse events and the patients were followed up till resolution or stabilization of AE.

Discussion

This study demonstrated that the test product, Hetero-rituximab was found non-inferior to reference medicinal product, Roche-rituximab. The primary analysis in the ITT population met the pre-specified non inferiority margin.

Rituximab as a monotherapy in FL patients had been studied in several randomized clinical studies in the past. Following the effectiveness of rituximab as a single agent treatment, rituximab was used in combination of chemotherapy in an attempt to improve long term outcome. Encouraging results from a phase II study of rituximab combined with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) prompted five pivotal trials to examine the benefit of adding rituximab to the chemotherapy regimen vs. chemotherapy alone. There were no clinically relevant changes in vital signs or biochemical parameters throughout the study. No significant differences were observed between the test and reference groups.

In this study, none of the analyzed samples, either in the Test or Reference group were found to be positive for anti-rituximab antibodies, i.e., immunogenicity was not observed with the study drugs.

Rituximab treatment leads to significant depletion in CD19+ cell which was comparable with reference and also with the values previously reported for reference rituximab.

Conclusion

Since difference between test and reference proportions of best overall response rate at Cycle 3, Cycle 6 and end study lies within the pre-specified limit for non-inferiority, it could be concluded that test product, a biosimilar of rituximab is also therapeutically similar to reference medicinal product FL patients.

References

8. Mabthera 100 mg and 500 mg concentrate for solution for infusion, Mabthera® Summary of Product Characteristic


