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# A REVIEW ON: NOVEL DRUG DELIVERY TECHNOLOGY OF RITUXIMAB

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## ABSTRACT

Rituximab can be used for the treatment of severe rheumatoid arthritis, *follicular lymphoma* phase III-IV, *follicular non-hodgkins lymphoma*, chronic lymphocytic leukimia therapy, advance therapy of *granulomatosis polyangiitis* and *microscopic polyitis*. Rituximab is a two compartment with an average half-life of 87 ± 18 hours and a volume distribution of 1.3L. Administration of rituximab at a dose of 375 mg / m2 in 4 consecutive weeks can increase serum drug concentration in each administration by infusion. This review article focuses on biosimilar technology of rituximab was carried out by increasing the teraupetic mechanism and the response to the potential effects of binding B-mAB in NHL disease. The development of biosimilar rituximab approved by the FDA, namely ofatumab (anti CD20) and Obinutuzumab (mAb from rituximab with a different glucose group).

**KEYWORD:** Rituximab, Biosimilar, NHL disease.

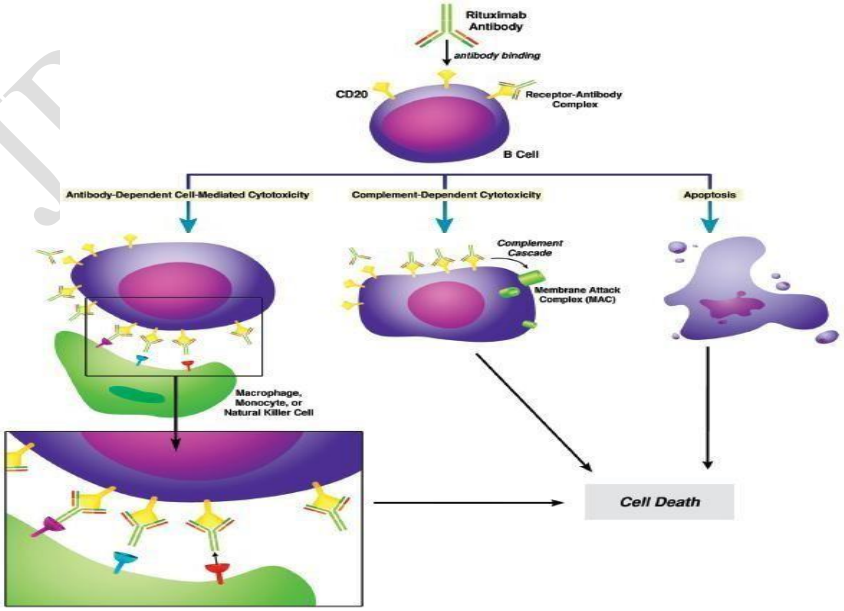
## FORMULATION

The use of Rituximab intravenously is given based on body surface area (BSA), dose calculation, and preparation using aseptic techniques. The disadvantage of using intravenous Rituximab is the use of an intravenous catheter and infusion-related reactions and patient discomfort. Therefore, a formulation of rituximab using subcutaneously developed with consideration of this administration can limit the volume of the drug to the level and number of drugs capable of reaching the vascular system and lymph tissue. The development of a drug delivery system, a highly concentrated rituximab formulation to reduce the volume of administration to 11.7 ml, but for its development required a reduction in the resistance that

occurs in sub-cutaneous administration. Human recombinant enzymes derived from DNA derivates (*alpha voryaluronidase*) were developed to overcome subcutaneous drug bioavailability barriers. By depolymerizing the viscoelastic component of the extracellular matrix (hyaluronan), *alpha voryaluroidase* reversibly alters the matrix structure and increases the rate of absorption of the drug and reduces locally injected drug resistance through conformation with *alpha vorhyaluronidase*. So that Rituximab administered subcutaneously at a fixed dose capable of achieving bioavailability is equivalent to the formulation of intravenous administration of Rituximab.[2]

## PHARMACOLOGY

Rituximab is a two compartment with an average half-life of 87 ± 18 hours and a volume distribution of 1.3L. $C_{max}$ concentration of rituximab is very dependent on the dose of the drug given. This is because the administration of rituximab at a dose of 375 mg / m2 in 4 consecutive weeks can increase serum drug concentration in each administration by infusion with a median value of Cmax of 239 to 460 µg / mL sequentially. Rituximab diffuses in the central nervous system (CNS) are not found in some organs such as the kidneys, lungs, liver, and lymph glands.[3] Rituximab is a monoclonal antibody drug that has an effect on B-cells and specifically on CD20 cell targets. CD20 cells are a typical part of only pre-B cells and mature B lymphocytes as shown in Figure 1. Rituximab will only bind to the CD20 cell portion of B lymphocyte cells by triggering the lymphocyte cell apoptosis process and eventually the cell dies.[4]




**Picture 1: Schemic Illustration of Rituximab Action Mechanism.[4]**

## CLINICAL USE

Rituximab can be used for the treatment of severe rheumatoid arthritis, *follicular lymphoma* phase III- IV, *follicular non-hodgkins lymphoma*, chronic lymphocytic leukemia therapy, advanced therapy of *granulomatosis polyangiitis* and *microscopic* polyitis[4].

## SIDE EFFECTS

Side effects that appear including fever, hypotension, bronchospasm, urticaria and angioedema. These side effects generally occur at 8% when administering the first infusion. In addition, rituximab can cause *Stevens-Johnson* reactions and *necrolysis* of cells in the epidermal part of the skin. Rituximab also has side effects such as infection with *Lysis* Syndrome, and hepatitis. In addition, rituximab can cause back pain, dizziness, and depression after drug use. Long-term use of rituximab can cause opportunistic infections such as *pneumonia, parvovirus B19, varicella, cytomegalovirus*, or the *herpes simplex* virus. Rituximab can cause *hepatitis-B* reactivation, which aggravates the condition of hepatitis and causes *hepatic failure*. In the use of rituximab, careful attention must be paid to the overall condition of the patient's body and monitoring of the condition of the patient.

## BIOSIMILAR OF RITUXIMAB

Biosimilar is a copy drug or similar biological product that has biological effects and activities such as available drugs or products or innovator drugs. Biosimilars are intended to increase security and effectiveness that are comparable or better than innovator products that have been *off-paten.*[5] Rituximab has several biosimilars can be seen in table 1.

**Table 1. Product Biosimilar Rituximab[6]**

| Biosimilar | Manufacturer | Drug Phase of Safety + Efficacy | Disease | Status | *Relative Cost Rituximab 500 $3.693 |
|---|---|---|---|---|---|
| BCD-020 (Alcebia) | Biocad (Rusia) | Approved | INHL | Launched | 72 % |
| BI 695500 | Boehringer Ing. (German) | Phase III | LTBFL | Terminated | - |
| PF-05280586 | Pfizer (USA) | Phase III | LTBFL | Recruiting | - |
| MK8808 | Merck Sharps &Dohme (EU) | Phase I | FL | Terminated | - |
| Mabal | Hetero (India) | Approved | CLL, DLCBL, FL | Launched | 87% |
| CT-P10 (Truxima) | Celltrion (South Korea) | Approved | ASFL | Launched | 72 % |

*ASFL, Advanced Stage Follicular Lymphoma. CLL, Chronic Lymphocytic Leukemia. DLBCL, Diffuse Large B-Cell*
*Lymphoma. FL,*
*Follicular Lymphoma. INHL, Indcient non-Hodgkin Lymphoma. LTBFL, Low Tumor Burden Follicular Lymphoma. *Price varies depending on the market and the country.*

## USE IN INDONESIA

Rituximab is included in several recommendations in setting standards for therapy related to the handling of specific diseases. Table 2. Concerning the Regulation of the Decree of the Minister of Health of the Republic of Indonesia Number HK.02.02 / MENKES / 523/2015, the National Formulary states that rituximab can be given to patients with certain conditions. Another regulation states that this drug can be given to patients with acute, moderate and severe levels of lymphoma and leukemia in the INA- CBG program included in the National Health Insurance program (JKN).[7,8] The treatment of lymphoma therapy can help in handling public health in Indonesia.

**Table 2: The use of Rituximab according to the regulations of KEPMENKES 2015.**

| Therapy | Dosage Form | Notes |
|---|---|---|
| For all types of Non-Hodgkins Lymphoma (LNH) with positive CD20 examination results. | Rituximab Inj. 10 mg/mL | Maximum prescription is 375 mg / m2 every 3 weeks. |
| For Chronic Lymphocytic Leukemia (CLL) therapy with positive CD20 examination results. | Rituximab Inj. 10 mg/mL | Maximum prescription is 375 mg / m2 every 3 weeks. |

## COST

The use of rituximab, according to Chaltron et al 2010, generally requires a cost of $ 630 to 10-mg / vial with a regimen dosage range ranging from 375 to 500 mg / m2 to 4 times of administration. This is of course adjusted to the desired dosage and therapy. However, the drug can be given up to 1000 mg for the treatment of rheumatoid arthritis. The price of rituximab is adjusted to markets available in certain countries.[4]

## RECENT DEVELOPMENT

The development of rituximab was carried out by increasing the therapeutic mechanism and the response to the potential effects of binding B-mAb in NHL disease, hence biosimilar rituximab approved by the FDA was developed, namely ofatumumab and obinutuzumab. Ofatumumab is an anti CD20 that is able to bind epitopes differently from CD20, whereas obinutuzumab is mAb from rituximab with a different glucose group.[6]

## CONCLUSION

Rituximab was discovered in 1975 and continued to be developed in 1980. This drug is continuously developed to be able to create the development of biosimilar drugs, namely *ofatumumab* and *obinutuzumab*. The use of rituximab is permissible for Indonesian society because it is supported by the government in the available MAB use options, and NHL therapy in particular. However, the use of rituximab needs therapeutic evaluation in its use, therefore, it can handle side effects well.

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