Clinical data TDM RITUXIMAB

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Theradiag
INNOVATION FOR BIOTHERAPIES

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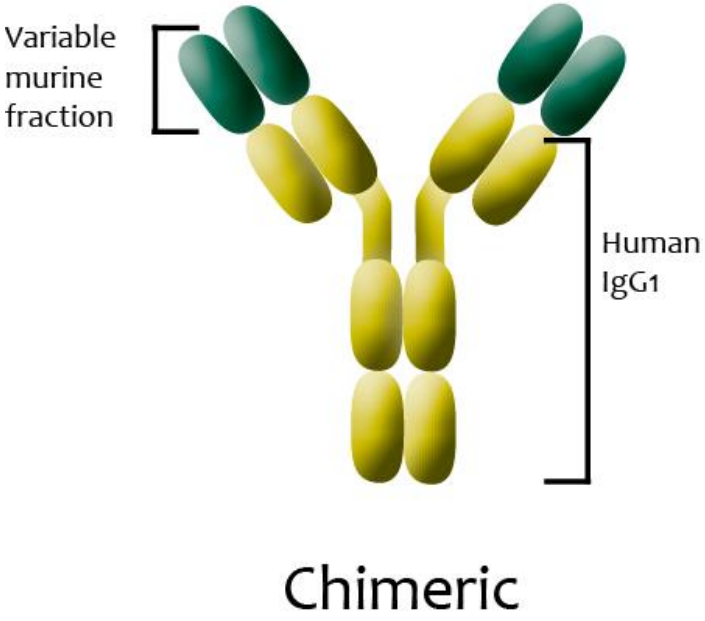
1

Introduction

RITUXIMAB



RITUXIMAB (RTX):

- Chimeric monoclonal antibody that targets the CD20 surface molecule (present on most B lymphocytes): induction of apoptosis, lysis by complement and antibody-dependent cell cytotoxicity (ADCC)
- **Brand name:** MabThera®
- Marketed by Roche
- **Marketing authorization:** FDA 1997 & EMA 1998
- RA: 931 patients *(data monitor 2017- France)*
  Oncology: 43,000 patients *(data monitor 2017- France)*
- Patent expired in 2013

RITUXIMAB - Biosimilars

Rituxan®	Biogen
Truxima®	CELLTRION
Riximyo®	SANDOZ
Ruxience®	Pfizer

RITUXIMAB – Indications

MabThera Rituximab

- Non-Hodgkin's lymphoma (NHL),
- Chronic lymphocytic leukemia (CLL),
- Rheumatoid arthritis (RA),
- Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MP),
- Pemphigus vulgaris

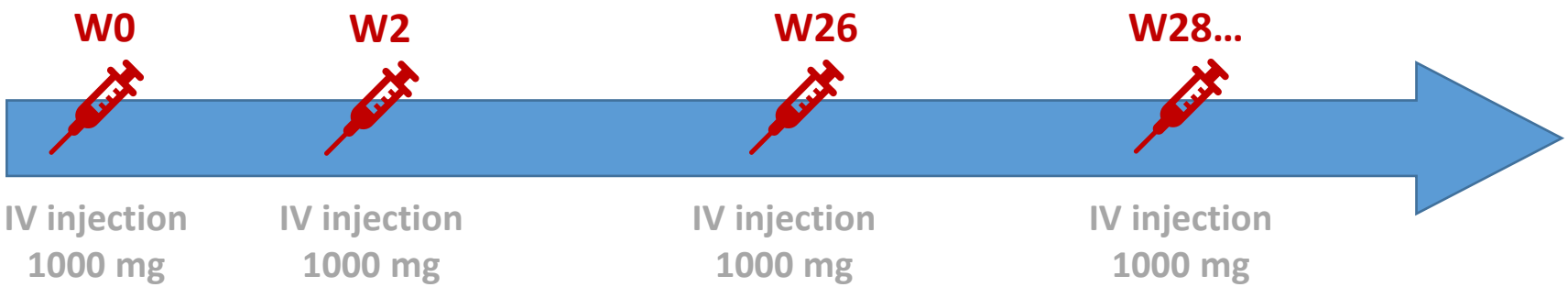
RITUXIMAB – Dosages

MabThera Rituximab

Indication	Recommandations
NHL	375 mg/m^2 body surface area/cure (1 injection/week)
CLL	Day 0 of the 1st cycle: 375 mg/m^2 body surface area Day 1 of each subsequent cycle: 500 mg/m^2 body surface area (6 cycles in total)
RA	2 IV infusions of 1000 mg at 2-week intervals
GPA & PAM	Induction: 375 mg/m2 body surface area once weekly for 4 weeks Maintenance: 2 IV infusions of 500 mg every 2 weeks followed by 1 IV infusion of 500 mg every 6 months
Pemphigus vulgaris	2 IV infusions of 1000 mg at 2-week intervals

EMA - 2021

RITUXIMAB: Simponi® - Administration protocol - RA



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Clinical trials – Rheumatoïd Arthritis

Correlation between serum rituximab level and clinical response in rheumatoid arthritis patients treated with B cell depletion therapy

- **Aims:** To investigate the relationship between serum RTX level just before a new re-treatment course and clinical response after 6 months.
- **Methods:** 25 consecutive RA patients treated with RTX for more than 12 months were included in this prospective study. Serum samples were collected for assay of drug level and anti-drug antibodies (ADAb) using sandwich ELISA.
- **Results:** Patients with detectable RTX level showed larger reduction of DAS28 and SDAI score at follow-up (P=0.0104, respectively P=0.0332), versus patients with undetectable RTX level.

- **Detectable RTX serum level just before re-treatment is correlated with further clinical response in RA patients.**
- **The results of the study are promising for the optimization of treatment responses and easily applicable in clinical practice.**

M. Diana et al – 2014 – BMJ Journals

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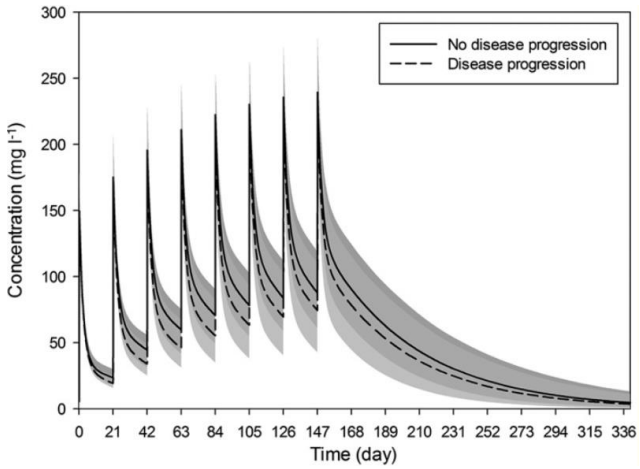
Clinical trials – Diffuse large B-cell lymphoma

Population pharmacokinetics of rituximab in patients with diffuse large B-cell lymphoma and association with clinical outcome

- **Aims:** To characterize rituximab PK in 29 newly diagnosed patients with diffuse large B-cell lymphoma (DLBCL) treated with rituximab and to evaluate the association of rituximab PK with clinical outcome.

- **Methods:** Rituximab serum levels were determined by ELISA and evaluated by a population PK analysis applying nonlinear mixed effects modelling.

- **Results:**



Association of time course of serum rituximab concentration with disease progression. Simulation was performed for a typical male patient (70 kg body weight, age 60 years) receiving standard therapy with rituximab (700 mg per cycle). Median predicted concentration (lines) and 90% prediction intervals (shaded areas)

- This finding indicates that time-changes in clearance could serve as a predictive marker of response to rituximab.
- The report demonstrates the rationale for studies evaluating higher doses of rituximab in selected patients.

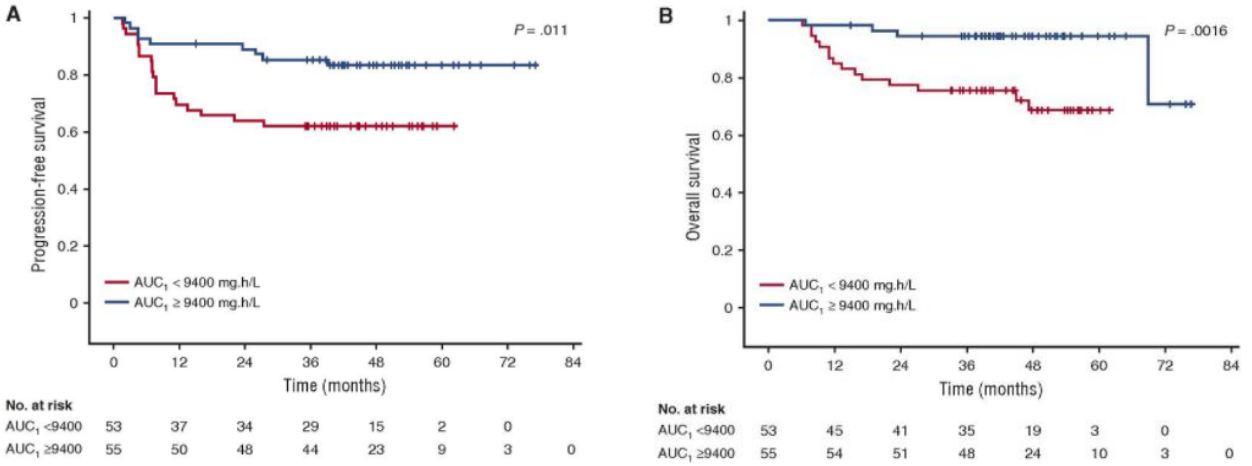
Rozman S. et al – 2017 – Br J Clin Pharmacol

Rituximab exposure is influenced by baseline metabolic tumor volume and predicts outcome of DLBCL patients: a LYSA study

- **Aims:** To quantify the influence of baseline total metabolic tumor volume ($TMTV_0$) on rituximab PK and of $TMTV_0$ and rituximab exposure on outcome in patients with DLBCL.

- **Methods:** $TMTV_0$ was measured by ^{18}F-fluorodeoxyglucose-positron emission tomography-computed tomography in 108 previously untreated DLBCL patients who received four 375 mg/m^2 rituximab infusions every 2 weeks in combination with chemotherapy in 2 prospective trials.

- **Results:**



- **Rituximab exposure is influenced by TMTV0 and correlates with response and outcome of DLBCL patients. Dose individualization according to TMTV0 should be evaluated in prospective studies**

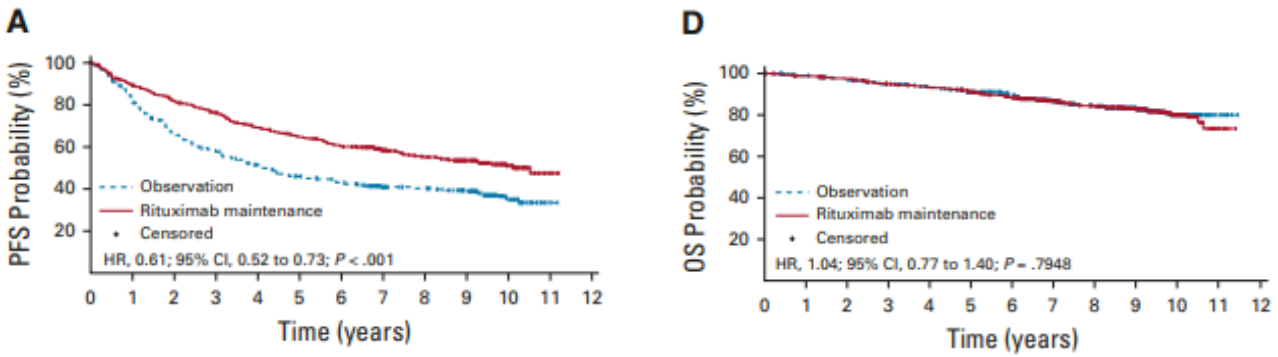
Tout M. et Al - 2017 - Blood

Sustained Progression-Free Survival Benefit of Rituximab Maintenance in Patients With Follicular Lymphoma: Long-Term Results of the PRIMA Study

- **Aims:** The PRIMA study established that 2 years of rituximab maintenance after first-line immunochemotherapy significantly improved progression-free survival (PFS) in patients with follicular lymphoma compared with observation.

- **Methods:** Patients (>18 years old) with previously untreated high-tumor-burden follicular lymphoma were nonrandomly assigned to receive one of three immunochemotherapy induction regimens. Responding patients were randomly assigned 1:1 to receive 2 years of rituximab maintenance (375 mg/m^2, once every 8 weeks), starting 8 weeks after the last induction treatment, or observation.

- **Results:**



- **Rituximab maintenance after induction immunochemotherapy provides a significant long-term PFS, but not OS (Overall Survival), benefit over observation**

Bachy E. et Al – 2019 – J Clin Oncol

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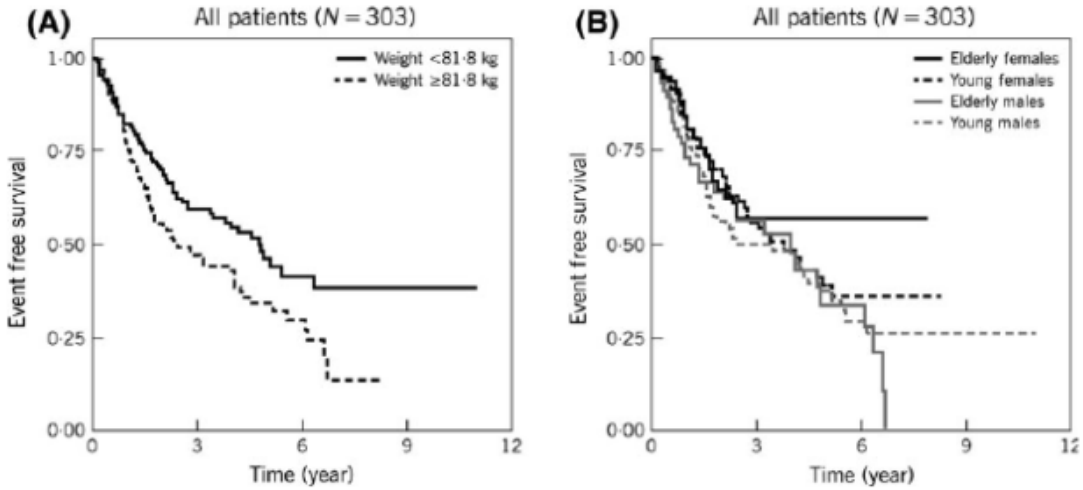
Clinical trials – Non-Hodgkin's lymphoma

Is rituximab sub-optimally dosed in indolent B-cell lymphoma?

- **Aims:** To analyze the effects of gender, age, weight and body surface area on rituximab pharmacokinetics and the outcomes on patients with indolent B-cell lymphoma (iNHL).

- **Methods:** Patients were divided into 3 treatment cohorts: rituximab only, rituximab + chemotherapy (R-CTX) and R-CTX followed by rituximab maintenance; furthermore, each cohort was subdivided as follicular (FL) or non-FL, based on histology

- **Results:**



Outcome of patients in all treatment cohorts combined according to weight (A) and age/gender (B). Patients who weighed ≥81.8 kg had inferior event-free survival (EFS). Elderly females had a trend towards better EFS compared with elderly males. Young males and females had similar outcome.

- **In conclusion, under current practices, a subset of patients with iNHL, i.e., follicular treated with RTX + chemotherapy, may be sub-optimally dosed with rituximab.**

Sawalha Y. et al - 2016 - Br J Haematol

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Clinical trials – Chronic Lymphocytic Leukemia

Rapid clearance of rituximab may contribute to the continued high incidence of autoimmune hematologic complications of chemoimmunotherapy for chronic lymphocytic leukemia

- **Hypothesis:** Despite the incorporation of rituximab into fludarabine-based chemotherapy regimens, the incidence of autoimmune cytopenia has remained high. Inadequate rituximab exposure due to rapid antibody clearance may be a contributing factor.

- **Methods:** Measure of the serum rituximab levels in patients treated with fludarabine and rituximab (375 mg/m^2).

- **Results:**
  - RTX through concentrations are not detectable at the end of the first cycle and raised during the other line treatments
  - RTX half-life varies according to tumor size
  - Dose optimization is feasible in patients developing effective autoimmune hemolysis

- **Rituximab is cleared so rapidly during the initial cycles of therapy for chronic lymphocytic leukemia that most patients have only transient serum levels. More frequent dosing of rituximab may be required to prevent autoimmune complications in at-risk patients**

- **RTX measurement enables to adapt dose optimization accordingly and avoid side effects**

Clifton C. Mo et al – 2013 – Haematologica

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Clinical trials – Pemphigus

Modified rheumatoid arthritis protocol for rituximab in pemphigus: a retrospective case series

- **Aims:** To investigate whether a modified RA protocol, in which the patient received a single treatment course ranging from 2 to 5 infusions of 1,000mg of rituximab during an interval of four weeks, is safe and effective in pemphigus management.

- **Methods:** Patients with pemphigus were treated with a single treatment course ranging from 2 to 5 infusions of 1,000mg of rituximab during an interval of four weeks. Clinical consensus late endpoints and desmoglein 1 and desmoglein 3 indices were monitored.

- **Results:** All 32 patients responded to therapy. Nineteen patients achieved complete remission during a median period of 46 weeks. Thirteen patients achieved partial remission during a median period of 46 weeks. The antidesmoglein index correlated well with clinical improvement in PV or PF.

- **Modified rheumatic arthritis protocol for rituximab was shown to be effective and safe in treating patients with pemphigus.**

Sakhiya J. et Al – 2020 – J Clin Aesthet Dermatol

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Clinical trials – Cytoplasmic anti-neutrophil antibody-associated vasculitis

Rituximab bioavailability in primary membranous nephropathy.

- **Aims:** To analyze rituximab bioavailability in a cohort of primary membranous nephropathy (MN) patients.
- **Methods:** A total of 43 patients with primary MN treated with two infusions of 1g rituximab at a 2-week interval were enrolled and followed for a median time of 39 months
- **Results:**

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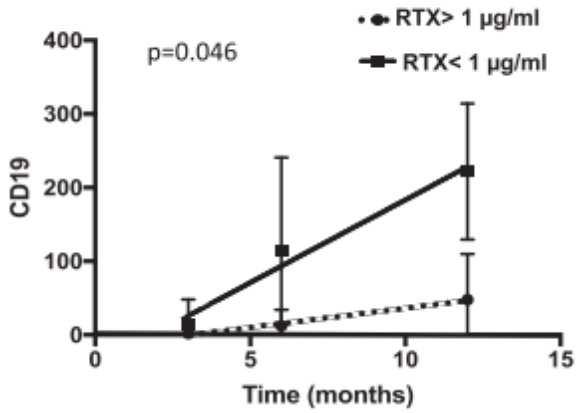


Count of CD19 at Months 3, 6 and 12 in two groups of MN patients according to their residual rituximab level at Month 3. In patients with low residual rituximab level (<1 µg/mL), B cells re-emerged more quickly (slope = 5.23 versus 22.45, P = 0.0465).

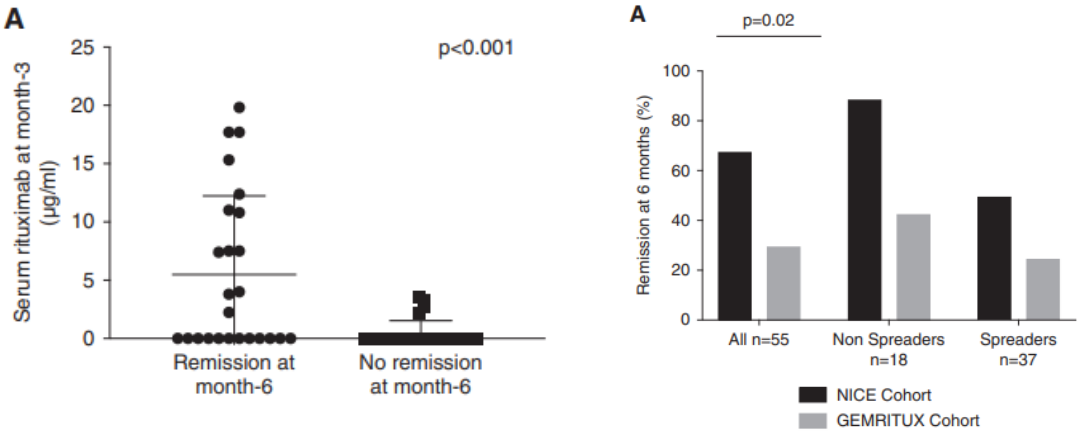
- **Higher residual serum RTX concentrations at Month 3 significantly correlated with higher B-cell depletion. Undetectable serum rituximab at Month 3 might be a useful biomarker for patients with active disease, which can predict resistance to rituximab and correlate with clinical outcomes.**

Boyer-Suavet S. et Al - 2019 - Nephrol Dial Transplant

High-Dose Rituximab and Early Remission in PLA2R1-Related Membranous Nephropathy.

Tracker

- **Aims:** To compare two protocols of rituximab in two prospective cohorts of anti-PLA2R1 positive patients.
- **Methods:** 28 participants from the NICE cohort received two infusions of 1-g rituximab at two-week intervals, whereas 27 participants from the GEMRITUX cohort received two infusions of 375 mg/m2 at one-week interval. We measured serum rituximab levels and compared remission at month six and before any treatment modification and analyzed factors associated with remission and relapses.
- **Results:**



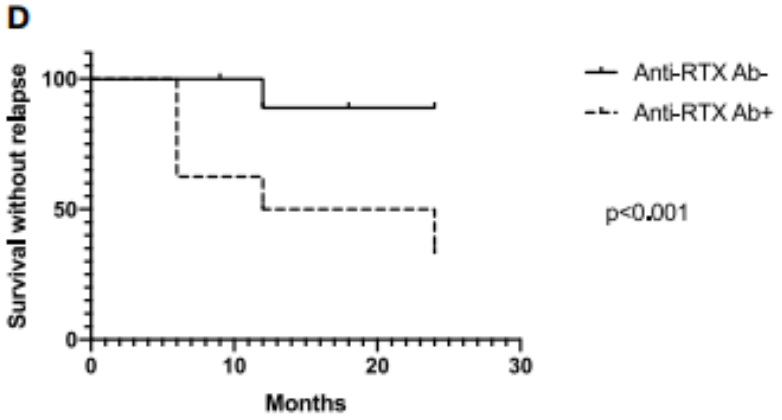
- Higher dose of RTX protocol is more effective on depletion of B-cells and lack of epitope spreading is associated with remission of membranous nephropathy
- Higher residual serum RTX levels at month 3 are associated with a higher rate of clinical remission

Seitz-Polski B. et Al – 2019 – Clin J Am Soc Nephrol

Neutralizing Anti-Rituximab Antibodies and Relapse in Membranous Nephropathy Treated With Rituximab

Tracker

- **Aims:** To analyze the relevance of anti-rituximab antibodies on the outcome of MN after a first course of rituximab.
- **Methods:** Forty-four MN patients were included and treated with two 1g infusions of rituximab at 2-weeks interval. Anti-rituximab antibodies, CD19 count, and clinical response were analyzed.
- **Results:**



The rate of relapse was significantly higher for patients with anti-rituximab antibodies ($p < 0.001$)

- Neutralizing anti-rituximab antibodies are not rare and their presence at month-6 is associated with subsequent relapses
- Anti-rituximab antibodies might be a useful biomarker adding to residual rituximab monitoring
- Humanized anti-CD20 seems to be a satisfying therapeutic alternative for patients with anti-rituximab antibodies and resistant or relapsing MN

Boyer-Suavet S. et Al – 2020 – Front. Immunol.

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Ongoing clinical trials

Rituximab maintenance treatment of newly diagnosed follicular lymphoma after Bendamustine or RCHOP or R2: a multicenter clinical study

- **Aims:** To evaluate the efficacy of rituximab maintenance treatment of newly diagnosed follicular lymphoma after induction therapy of BR, RCHOP or R2.

- **Methods:**
  1. BR+R → rituximab combined with bendamustine (BR) maintenance treatment
  2. RCHOP+R → rituximab combined with cyclophosphamide, vincristine, doxorubicin, prednisone maintenance treatment
  3. R2+R2 → Lenalidomide combined with rituximab maintenance treatment

- **Outcomes:**
  1. Minimal residual disease (MRD) negative of bone marrow at 24 weeks
  2. Overall response rate
  3. Overall survival
  4. Progression of disease within 24 months
  5. Event-free survival

Ruijin Hospital – Zhao Weili

Pharmacokinetic study of rituximab induction regimen in ANCA-associated vasculitis (MONITUX)

- **Aims:** To evaluate whether monitoring serum rituximab levels could be an interesting tool in the follow-up of ANCA-associated vasculitis patients.

- **Methods:** Classical induction regimen with rituximab, implying an infusion of 375mg/m^2 per week, for 4 consecutive weeks with blood specimen. Serum rituximab levels (along with serum anti-rituximab antibodies levels) will be determined (at M+1 and M+3) and the correlation with clinical outcome at M+6 will be analyzed.

- **Outcomes:**
  1. Serum rituximab levels (1, 3 & 6 months after stop of rituximab induction regimen)
  2. Serum anti-rituximab antibodies (1, 3 & 6 months after stop of rituximab induction regimen)
  3. Serum B lymphocytes ($CD19^+$ cells) levels (1, 3 & 6 months after stop of rituximab induction regimen)

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Take home messages

Summary

MabThera Rituximab

- ✓ **Rituximab or MabThera® →** Chimeric monoclonal antibody that targets the CD20 surface molecule
- ✓ **Indications →** Non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MP), pemphigus vulgaris
- ✓ **Dosages**

Indication	Recommendations
NHL	375 mg/m^2 body surface area/cure (1 injection/week)
CLL	Day 0 of the 1st cycle: 375 mg/m^2 body surface area Day 1 of each subsequent cycle: 500 mg/m^2 body surface area (6 cycles in total)
RA	2 IV infusions of 1000 mg at 2-week intervals
GPA & MP	Induction: 375 mg/m2 body surface area once weekly for 4 weeks Maintenance: 2 IV infusions of 500 mg every 2 weeks followed by 1 IV infusion of 500 mg every 6 months
Pemphigus vulgaris	2 IV infusions of 1000 mg at 2-week intervals

- A detectable serum RTX level correlates with a more advanced clinical response in RA patients.
- Rituximab exposure correlates with response and outcome in patients with DLBCL.
- Higher residual serum RTX levels at month 3 are associated with a higher rate of clinical remission.