Rituximab in Nephrology

Mechanism of action
Indications
Side effects

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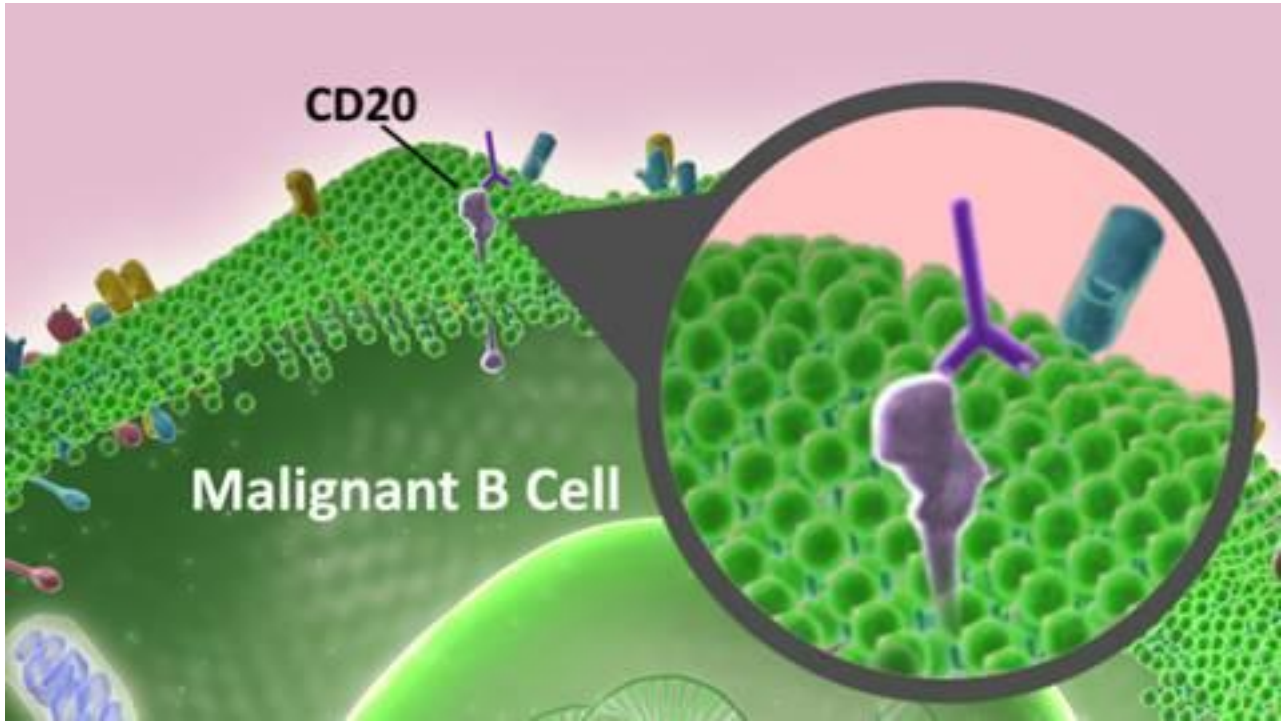
30 June 22

Rituximab a B-cell depleting monoclonal antibody.



https://en.wikipedia.org/wiki/Rituximab

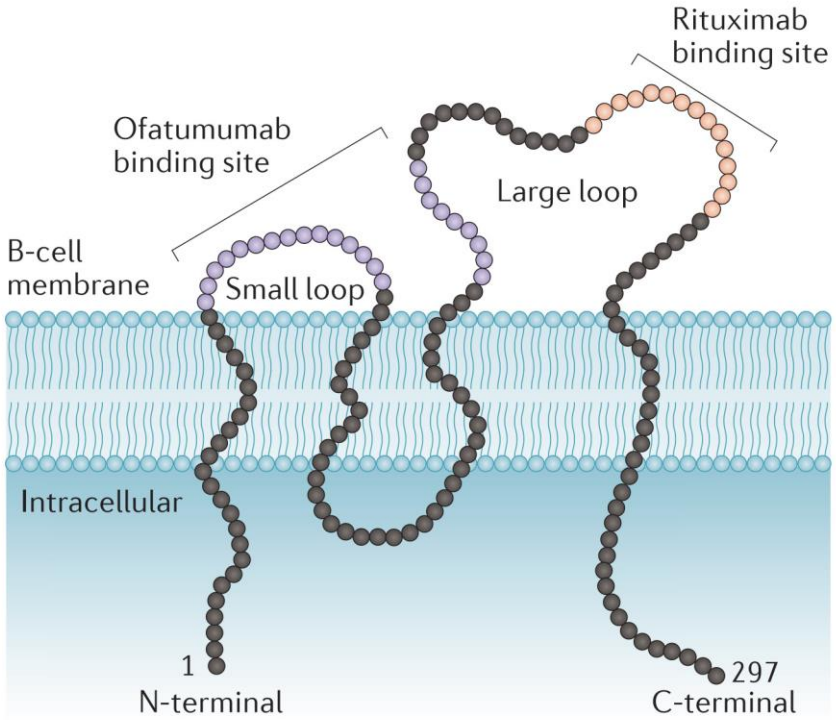


Figure 4 | **The molecular configuration of the CD20 molecule.** CD20 is a tetra-transmembrane protein that essentially remains on the membrane of B cells without dissociation or internalization upon antibody binding. CD20 has small and large extracellular loops. The binding sites of CD20 monoclonal antibodies, rituximab and ofatumumab, are indicated. Rituximab binds an epitope on the large loop only, whereas ofatumumab specifically recognizes an epitope encompassing both the small and large extracellular loops of the CD20 molecule.

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Treatment of membranous nephropathy: time for a paradigm shift

Piero Ruggenenti[1,2], Fernando C. Fervenza[3] and Giuseppe Remuzzi[1,2,4]

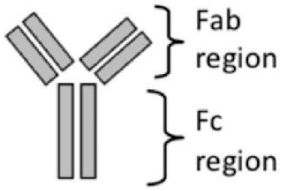
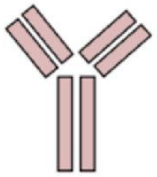
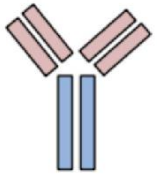
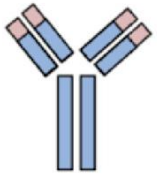
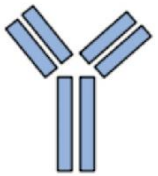
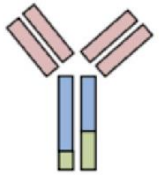
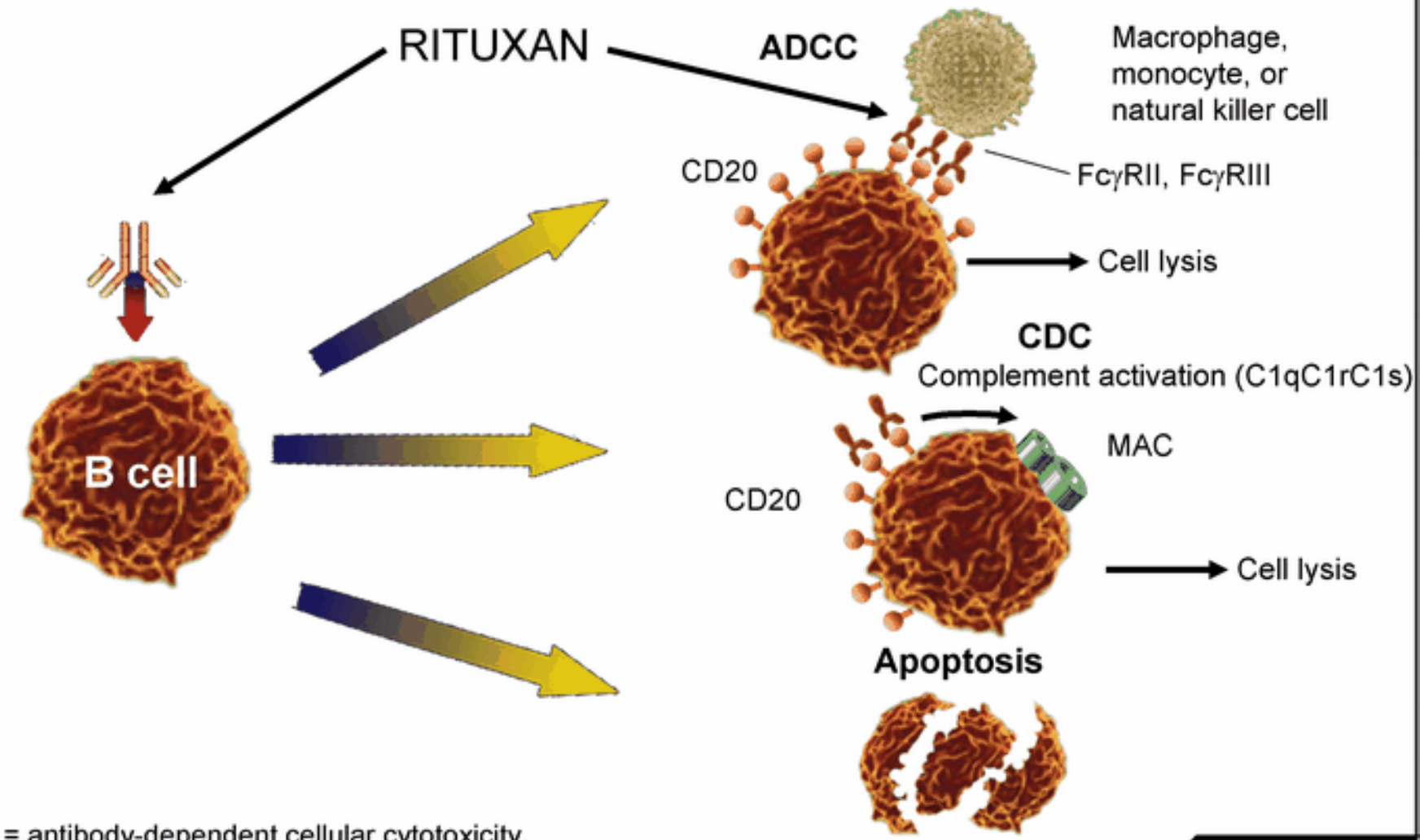
Generation	1st Generation		2nd Generation		3rd Generation
mAb Structure 	Murine (100% rodent)  Suffix: -***o***mab	Chimeric (65% human)  Suffix: -***xi***mab	Humanised (>90% human)  Suffix: -***zu***mab	Fully human  Suffix: -***u***mab	Modified Fc region (chimeric or humanised) 
Immunogenicity	Higher → Lower				
Anti-CD20 mAbs	*Not in clinical use due to short half-life, poor efficacy and high risk of adverse reactions*	**Rituximab** Biosimilars: **Truxima** **Rixathon** *Unlicensed use in neurology (table 2)*	**Ocrelizumab** *Licensed for relapsing and primary progressive MS*	**Ofatumumab** *Currently in phase III clinical trials for MS*	**Ublituximab (TG-1101)** (chimeric) *Currently in phase III clinical trials for MS*
Anti-CD19 mAbs					**Inebilizumab (MEDI-551)** (humanised) *Currently in clinical trials for MS and NMOSD*

Figure 2 B-cell-depleting monoclonal antibodies in neurology. mAb, monoclonal antibody; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

RITUXAN

Mechanism of Action



ADCC = antibody-dependent cellular cytotoxicity.
CDC = complement-dependent cytotoxicity.

biogen idec

http://blogs.shu.edu/cancer/2014/07/23/monoclonal-antibodies-kinase-inhibitors-are-better-than-antibodies-alone-in-breast-cancer-and-b-cell-lymphoma/

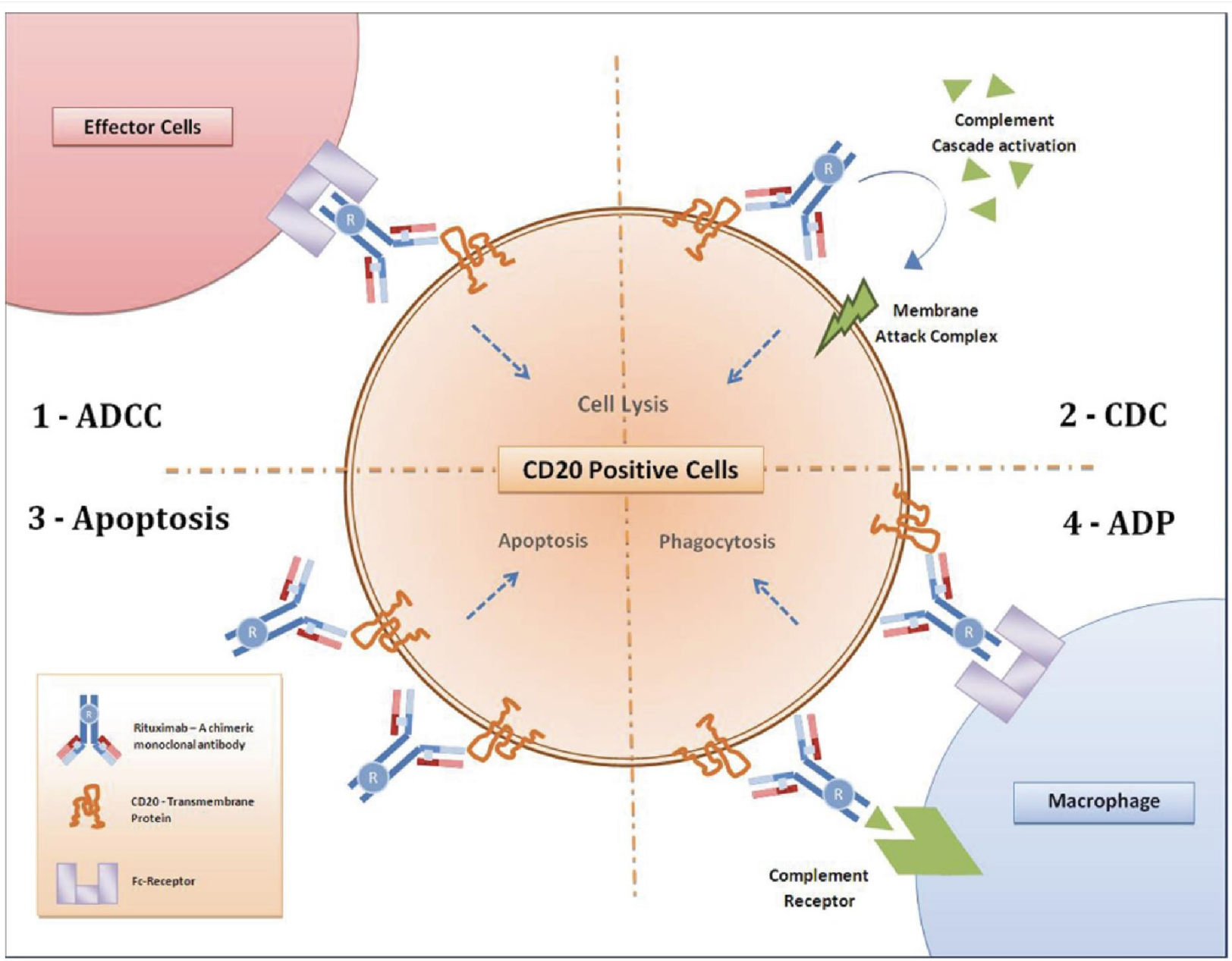


Figure 1. The proposed mechanisms of action for rituximab, a chimeric monoclonal antibody, against the CD 20 receptor. (1) Antibody-dependent cell-mediated cytotoxicity (ADCC). Effector cells include natural killer cells and phagocytic cells such as monocytes and macrophages that express Fc receptors. (2) Complement-dependent cytotoxicity (CDC). (3) Direct effects of binding (induction of apoptosis and sensitization to other chemotherapeutic agents). (4) Antibody-dependent phagocytosis (ADP).

CRITICAL CARE
REVIEW
Kasi et al. Critical Care 2012, 16:231
http://ccforum.com/content/16/4/231

Clinical review: Serious adverse events associated with the use of rituximab - a critical care perspective

Pashtoon M Kasi[1], Hussein A Tawbi[2], Chester V Oddis[3] and Hrishikesh S Kulkarni*[1]

Table 1. Common indications for rituximab therapy

Disease conditions
Chronic lymphocytic leukemia
CD20+ non-Hodgkin lymphoma (expressing the B-lymphocyte antigen CD20)
Rheumatoid arthritis
Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis
• Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)
• Microscopic polyangiitis
• Eosinophilic granulomatosis associated with polyangiitis (formerly Churg-Strauss syndrome) (unlabeled)
Chronic refractory graft-versus-host disease (unlabeled)
Refractory idiopathic thrombocytopenic purpura (unlabeled)
Hodgkin lymphoma (unlabeled)
Refractory pemphigus vulgaris (unlabeled)
Post-transplant lymphoproliferative disorder (unlabeled)
Waldenström macroglobulinemia (unlabeled)
Type I diabetes mellitus (unlabeled)
Multiple sclerosis (unlabeled)
Renal transplant (unlabeled)

Table 2. Common terminology Criteria for Adverse Events Version 4.0 (CTCAE) [31]

Grade of toxicity	Brief description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to adverse event

[a]'Instrumental ADL' refers to activities of daily living such as preparing meals, shopping for groceries or clothes, using the telephone, and managing money. [b]'Self-care ADL' refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden. From the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. May 29, 2009 NIH publication #- 09-7473.

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REVIEW

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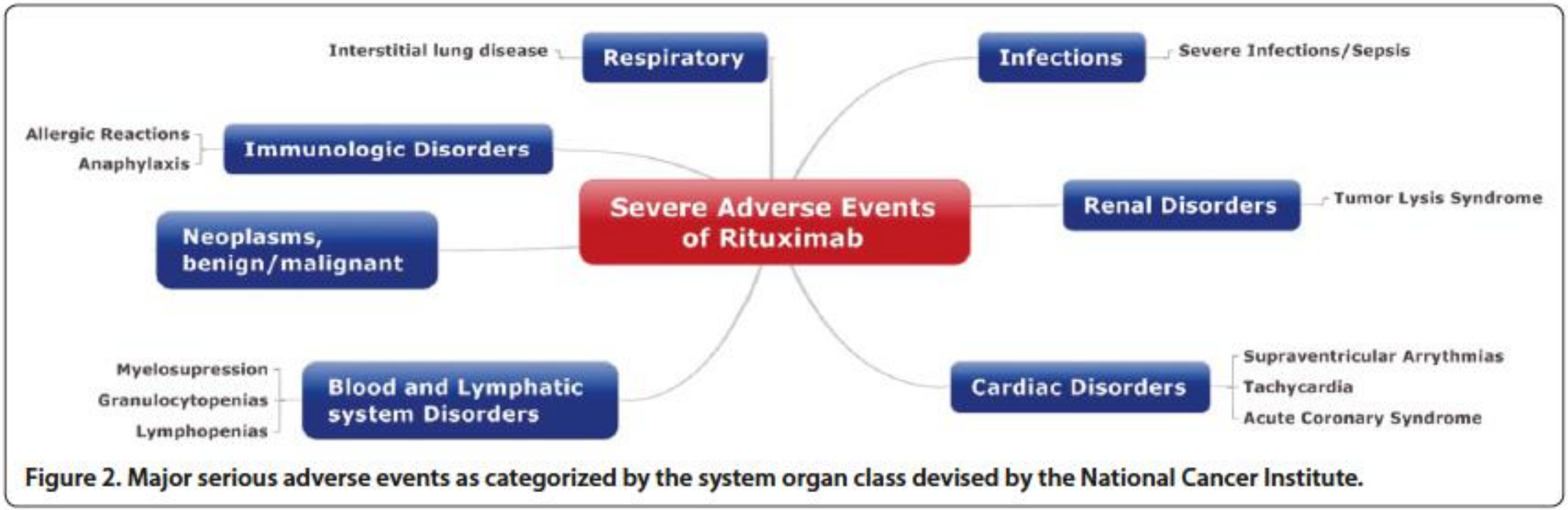

Figure 2. Major serious adverse events as categorized by the system organ class devised by the National Cancer Institute.

Kasi *et al. Critical Care* 2012, 16:231
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CRITICAL CARE

REVIEW

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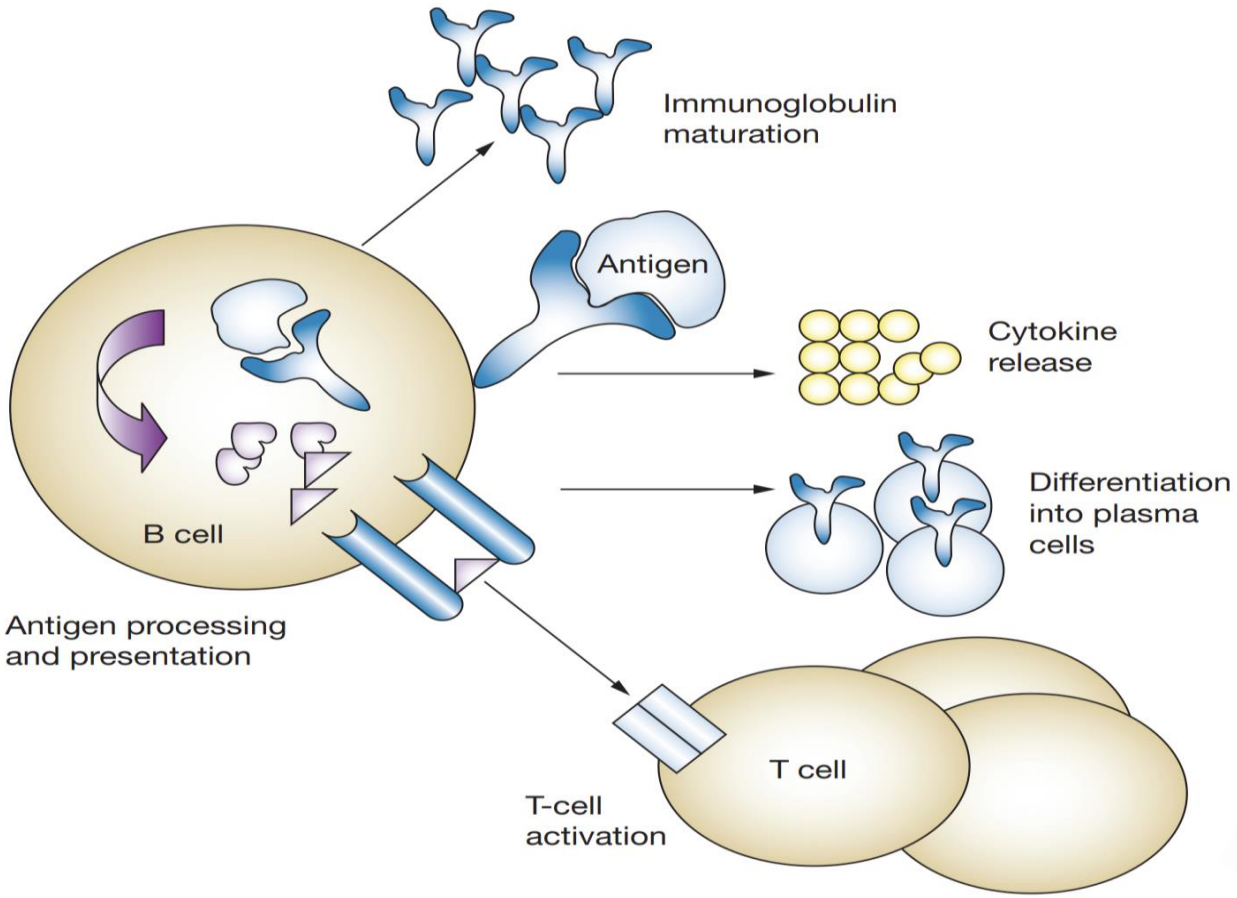

Figure 2 B-cell functions are inhibited following cell depletion by rituximab. Following activation, B cells produce cytokines, modify immunoglobulin production, process antigen for presentation to T cells, and proliferate and differentiate into plasma cells. Rituximab perturbs these processes.

REVIEW

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Drug Insight: rituximab in renal disease and transplantation

Alan D Salama* and Charles D Pusey

Table 1 Reported adverse effects attributed to rituximab therapy in autoimmune and hematological disease.[b–e]

Category	Adverse effect	Frequency[a] (%)	References
Infusion[b]			
	Rigors, chills	10	Keogh *et al.* (2006)[31]
	Fever, headache	13	Pijpe *et al.* (2005)[60]
	Dyspnea	20	Keogh *et al.* (2006)[31]
	Hypotension	10	Kimby (2005)[61]
	Bronchospasm	5–10	Looney *et al.* (2004)[7], Kimby (2005)[61]
	Angioedema	8–9	Ruggenenti *et al.* (2003)[10], Keogh *et al.* (2005)[26]
	Rash	2–8	Edwards *et al.* (2004)[5], Ruggenenti *et al.* (2003)[10], Keogh *et al.* (2006)[31]
Short term (6 months) infectious[c]			
	URTI	9–50	Keogh *et al.* (2005)[26], (2006)[31]
	Herpes zoster	7–20	Keogh *et al.* (2006)[31]
	Influenza	10	Keogh *et al.* (2006)[31]
HACA			
	HACA only	0–50	Edwards *et al.* (2004)[5], Keogh *et al.* (2006)[31], Pijpe *et al.* (2005)[60]
	HACA with serum sickness	20	Pijpe *et al.* (2005)[60]
Other			
	Abdominal pain	17	Choquet *et al.* (2005)[56]
	Purpura	2–13	Choquet *et al.* (2005)[56], Keogh *et al.* (2006)[31], Pijpe *et al.* (2005)[60]
	Retinal artery thrombosis	6	Zaja *et al.* (2003)[15]
	Myalgia	2–20	Choquet *et al.* (2005)[56], Pijpe *et al.* (2005)[60]
	Neutropenia	4–14	Choquet *et al.* (2005)[56], Kimby (2005)[61]
	Thrombocytopenia[d]	9	Kimby (2005)[61]
Long term (>6 months)			
	Adenocarcinoma	2	Garrett *et al.* (2005)[62]
	Neutropenia[e]	0.02	Kimby (2005)[61]

[a]Most series of patients with autoimmune disease are small, which would exaggerate reported frequencies. Confounding effects of concurrent therapeutic agents must also be considered. [b–e]From hematological series adverse effects reported were as follows: [b]up to 71% of patients have a mild reaction to first infusion (severity decreases with subsequent infusions; [c]19% bacterial, 10% viral, 1% fungal; [d]generally transient but can be delayed in rare cases; [e]based on studies of rituximab in hematological conditions.
HACA, human antichimeric antibodies; URTI, upper respiratory tract infection.

REVIEW

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Box 1 Rituximab protocols for treatment of renal disease.

Standard
Four weekly infusions (375 mg/m^2) for non-Hodgkin's lymphoma, cryoglobulinemia (in association with hepatitis C virus infection), systemic lupus erythematosus, idiopathic membranous nephropathy and pure red cell aplasia

Prolonged
Eight weekly infusions (375 mg/m^2) for non-Hodgkin's lymphoma and cryoglobulinemia

Extended
Standard dosing regimen plus two or three monthly infusions (375 mg/m^2) for nephrotic syndrome and idiopathic membranous nephropathy

Modified short
Two 2-weekly infusions (1 g per infusion) for anti-neutrophil cytoplasmic autoantibody-associated vasculitis and systemic lupus erythematosus

Single dose
One infusion (50–375 mg/m^2) for transplant rejection, reduction of preformed alloantibodies or anti-blood-group antibodies

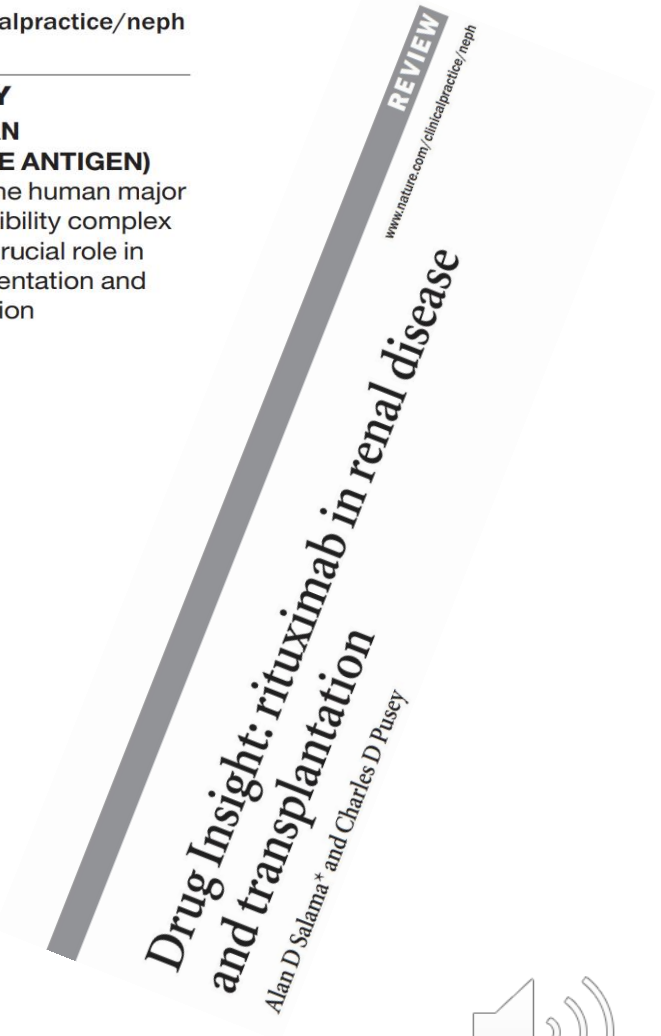
Box 2 Immune effects of B-cell depletion by rituximab.

- Evidence that rituximab affects production of antibodies and regulation of immunoglobulin maturation by B cells includes reduced levels of IgM (variable), rheumatoid factor and autoantibodies (variable)
- Evidence that rituximab affects cytokine production by B cells includes reports of cytokine-release syndromes in patients with hematological disease, which potentially accounts for some infusion-related adverse effects. No evidence for alteration in B cell cytokine profiles is available
- Evidence that rituximab affects T-cell activation by B cells includes reduced T-cell expression of HLA-DR, CD154 and CD69
- Evidence that rituximab affects lymphocyte homeostasis mediated by B cells includes normalization of lymphocyte subsets in active systemic lupus erythematosus
- There are few data to support an effect of rituximab on antigen presentation by B cells

Note: few data regarding the mechanisms of action of rituximab in autoimmune disease are available.

GLOSSARY

HLA (HUMAN LEUKOCYTE ANTIGEN)
Proteins of the human major histocompatibility complex that have a crucial role in antigen presentation and T-cell activation



Part 1: Planning a single or first treatment course

Rituximab in neurological disease: principles, evidence and practice Whittam DH, et al. Pract Neurol 2019;19:5–20. doi:10.1136/practneurol-2018-001899

Exclude contra-indications:

1. Hypersensitivity to rituximab or murine proteins.
2. Active, severe infection (e.g. TB, sepsis, opportunistic infections).
3. Severe immunocompromised state*.
4. Severe heart failure or uncontrolled cardiac disease.

** CD3, CD4, CD8, CD19, CD20 and CD56 cell counts can be assessed and discussed with immunology when concerned.*

Mandatory pre-treatment work-up:
- Emergency and elective use (eg, anti-NMDAR encephalitis)

Informed written consent for unlicensed administration.
Patient information sheet (supplementary online material 1).

Blood tests:

- Full blood count.
- Liver function tests.
- Immunoglobulin levels
  - subnormal levels do not preclude treatment.
- HBV serology (HBV surface antigen and core antibody)
  - if either is positive, seek expert opinion and start anti-viral prophylaxis before rituximab treatment.
- *HCV and HIV serology.*

Additional pre-treatment work-up:
- If elective maintenance therapy planned (eg, NMOSD)

- Discuss contraception.
- Take immunisation history and give necessary vaccines*
  - give non-live vaccines >4 weeks, live vaccines >8 weeks prior to first infusion.
- *Give pneumococcal vaccine to all patients if possible.*
- *Test for latent TB in high-risk groups (QuantiFERON-TB Gold or tuberculin skin testing, followed by chest radiograph if indicated).*
- *VZV serology if there is no history of primary infection.*

** In uncertain cases, antibody titres could be obtained for important vaccines.*

Part 2: Infusion day (see infusion checklist, supplementary online material 2)

On the day of infusions:	1. Withhold morning antihypertensive medications if possible. 2. Verify consent. 3. Clinical assessment to exclude active infection. 4. Pregnancy test if appropriate.
Administration:	1000 mg on day 1 and day 15 *or* 375 mg/m^2 body surface area weekly for 4 weeks. Give intravenous methylprednisolone 100 mg prior to each infusion.

BMJ
Whittam DH, et al. Pract Neurol 2019;19:5–20. doi:10.1136/practneurol-2018-001899

REVIEW

Rituximab in neurological disease: principles, evidence and practice

Daniel H Whittam,[1] Emma C Tallantyre,[2,3] Stephen Jolles,[4,5] Saif Huda,[6] Robert J Moots,[6] Ho Jin Kim,[7] Neil P Robertson,[2,3] Bruce A C Cree,[8] Anu Jacob[1,9]

Part 3: Re-treatment (usually for relapsing disease)

Rituximab in neurological disease: principles, evidence and practice
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Option 1 **UK NMO Service practice** adapted from Greenberg *et al* [63]	Monitor circulating B-cell count ($CD19^+$ cells) monthly. Retreat with single 1000 mg infusion when it rises above 1%*. ** Consider tighter re-treatment threshold (0.05%) if breakthrough disease occurs.*
Option 2 **Developed for NMOSD** Kim *et al* [4 67]	Monitor memory B-cell population ($CD19^+/CD27^+$ cells*) six weekly in first year, eight weekly in second year, 10 weekly thereafter. Retreat with 375 mg/m^2 when it rises above 0.05% in the first 2 years and 0.1% thereafter. ** Very small cell population – discuss with laboratory regarding feasibility and cost*
Option 3 **If B-cell monitoring is not possible**	Repeat either single infusions or treatment courses at regular 6 month intervals.

Work-up prior to subsequent infusions:

- *Baseline full blood count.*
- *Check immunoglobulin levels if there is history of recurrent infection, or in high risk patients for secondary antibody deficiency (including low baseline IgG, previous immunosuppression, combination therapy).*
- *Consider further investigations from part 1 if clinically indicated (eg, risk of exposure to viral hepatitis).*

Figure 4 Rituximab administration guide. *Italicised points reflect our personal practice rather than established recommendations.* HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NMDAR, N-methyl-D-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorders; TB, tuberculosis; VZV, varicella zoster virus.

Table 2 Other considerations and special circumstances when prescribing rituximab

Circumstance	Known risks	Recommended management
Pregnancy	The safety of B-cell-depleting biologic therapies is not fully known. In 153 exposed pregnancies, rates of miscarriage and congenital malformation were similar to expected rates in the general population.[82] Placental transfer of immunoglobulins (including rituximab) occurs from the second trimester onwards. Exposure during organogenesis is therefore likely to be very limited. Exposure in later pregnancy has resulted in neonatal B-cell depletion, which recovered in 3–6 months.[82]	Effective contraception (in both sexes) is advised by manufacturers during and for 12 months after treatment.[6 56] Avoid in pregnancy unless potential benefit to the mother outweighs risk of B-cell depletion in the fetus[6 56] (see the text section 'risks and adverse events' for further discussion). Live vaccines should not be given to exposed babies for the first 6 months of life. *We counsel women before starting rituximab and perform a pregnancy test before each infusion.*
Breast feeding	There are no studies formally assessing safety of rituximab during lactation. As a large molecule, it is unlikely to transfer to breast milk in any significant amounts. The exception to this is the first 3 days post partum when gaps between breast alveolar cells are larger and transfer of immunoglobulins is possible. Rituximab has poor gastrointestinal absorption and is likely be destroyed in the baby's gut.[92]	Despite apparent low risks there is still insufficient evidence to guarantee safety. Manufacturers advise that women avoid breast feeding during and for 12 months after treatment.[6 56] *We counsel mothers and support their decision if they choose to breast feed.*
Existing cardiac disease	Severe cardiac disease is a contraindication to rituximab when used for rheumatoid arthritis or ANCA-associated vasculitis (but not lymphoma) due to a higher risk of myocardial infarction, arrhythmia or decompensating severe heart failure.	Consider alternative treatment options in patients with severe uncontrolled cardiac disease.
Previous hepatitis B virus (HBV) infection	Risk of HBV reactivation after rituximab is well described and includes fatal cases of fulminant hepatitis.[93] Reactivation can occur in both HBVsAg-positive and HBVsAg-negative HBVcAb-positive patients ('reverse seroconversion').[93]	Do not give rituximab to patients with active HBV hepatitis. Test HBVsAg, HBVcAb and liver function tests in all patients prior to starting rituximab.[93] Refer those with positive serology to a specialist for prophylactic antiviral therapy, which must be continued for the duration of therapy. Monitor these patients with serial HBV DNA titres, liver function tests and HBVsAg (if HBVsAg negative at baseline).[94]
Previous hepatitis C virus (HCV) infection	Information is conflicting but reactivation of HCV seems to be much less common than HBV. Increases in HCV RNA load and hepatic flares are reported, but many cases are confounded by additional immunosuppressive/hepatotoxic medications.[95 96]	*We recommend screening for HCV antibody prior to starting treatment. Positivity is not a contraindication to rituximab but we suggest such patients should be jointly managed with hepatology and monitored for HCV activity (HCV RNA titres and liver function tests).*
Previous/latent tuberculosis (TB)	Risk of TB reactivation after rituximab appears negligible,[97] though coadministration with glucocorticoids may contribute additional risk.	Do not give rituximab in cases of active TB. *Although routine TB screening may be unnecessary,[98] we screen for latent TB with QuantiFERON-TB Gold or tuberculin skin testing in high-risk patients (eg, from endemic regions).*
Vaccinations	There is a theoretical risk that live vaccines (eg, yellow fever, varicella-zoster) may cause infection. Other standard inactivated vaccines are safe but they may be less effective after receiving rituximab.[99 100]	Where possible give all routine vaccinations at least 4 weeks prior to initiating rituximab (and at least 8 weeks prior for live vaccines).[56 98] Do not give live vaccines to patients treated with rituximab. *We recommend annual influenza vaccine and five-yearly pneumococcal vaccine throughout treatment.*

Italicised points reflect personal practice rather than established recommendations.
ANCA, antineutrophil cytoplasmic antibody; HBVcAb, hepatitis B virus core antibody; HBVsAg, hepatitis B virus surface antigen.

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Table 3 Rituximab treatment risks and management. Unless a separate reference is given, information is adapted from MabThera SmPC [56], experience from RA

Risk	Description	Recommended management
Infusion reactions	The highest risk is with the first infusion (~30%). Most reactions are mild (headache, pruritus, throat irritation, flushing, rash, urticaria, fever, hypo/hypertension). Severe or life-threatening anaphylactoid infusion reactions leading to drug discontinuation are uncommon (<1/100 cases). Pretreatment with corticosteroids reduces the frequency and severity of reactions.	*If possible, withhold antihypertensive medications on the morning of the infusion.* Adhere to manufacturers' advice regarding infusion rates. Unless contraindicated, give intravenous methylprednisolone 100 mg before the infusion. Manage mild reactions with interruption or slowing of infusion, paracetamol and antihistamine. Restart infusion at a reduced rate once symptoms resolve. Manage severe reactions as per the Advanced Life Support algorithm. Have necessary equipment and medications available.
Mucocutaneous reactions	Severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis occur very rarely following rituximab infusion, some with fatal outcome (<1/10 000 cases).	Do not re-treat with rituximab if the patients develops a severe skin reaction.
Adverse cardiac events	Rituximab is not directly cardiotoxic but angina pectoris, arrhythmias and heart failure rarely occur (<1/1000 cases).	Consider alternative treatment options in patients with severe uncontrolled cardiac disease. Manufacturers recommend 'close monitoring' of those with known cardiac disease.
Infections	Most infections are mild to moderate, consisting of upper respiratory tract and urinary tract infections (very common, >1/10 cases). Bronchitis, sinusitis and gastroenteritis occur in 1/100-1/10 cases. Serious opportunistic infections are rare, including reactivation of hepatitis B. Hypogammaglobulinaemia and neutropenia may contribute to infection risk in some cases (see below).	Do not give rituximab to patients with active infection. Ask and counsel patients regarding infection or risk of infection. *We recommend annual influenza vaccine and five-yearly pneumococcal vaccine throughout treatment.* See notes in table 2 regarding specific infectious risks: hepatitis B, C and tuberculosis.
Secondary antibody deficiency	Decreased IgM levels are very common; decreased IgG levels are common. Hypogammaglobulinaemia seems to be time and dose dependent.[78 79] Prior exposure to immunosuppressant drugs may be an additional risk factor.[81 88] Patients with low IgG are at risk of infection, particularly recurrent bacterial sinopulmonary infections, but risk does not correlate directly with IgG level.[78 81] Patients with low baseline IgG levels are at particular risk of infection.[80]	*Check baseline total serum immunoglobulin levels prior to starting rituximab. Be aware of higher infection risk in patients with low IgG and consider alternative options. Recheck serum Ig in the context of severe or recurrent infections. See Box 1 for approach to symptomatic secondary antibody deficiency.* *Consider checking IgG levels in patients with a history of immunosuppressive medication use before retreatment with rituximab.*
Neutropenia	May occur after first or subsequent infusions. The highest risk is 3–6 months after infusion. Prevalence of 1.3%–2.3% when rituximab is given for autoimmune indications[101]; reported in MS and NMOSD.[102–104] The severity and duration of neutropenia is unpredictable. Many cases are asymptomatic and self-limiting but grade IV neutropenia (<0.5/10^9/L) with severe infection is rarely reported.	Check full blood count prior to administering rituximab and on symptoms or signs of infection. *Observe cases of asymptomatic mild neutropenia. G-CSF has been used to hasten recovery in grade IV neutropenia or sepsis.*[104] Though it may recur, neutropenia is not a contraindication to ongoing rituximab therapy—several case series support ongoing use in autoimmune disease.[101 103–105]
PML	Rituximab may increase risk of PML in individuals already at risk due to pre-existing conditions or immunosuppression. Risk is estimated at 1 in 30 000 cases exposed to rituximab.[106] No cases have yet been described when rituximab is used alone to treat neuroinflammatory disease.	Discuss progressive multifocal leucoencephalopathy risk during consent process. JCV antibody titres do not have an established role in rituximab use. *MRI if suggestive clinical features develop.*
PRES	Described following rituximab administration in NMOSD and non-neurological indications. Prevalence of 0.5% in a large cohort of patients with NMOSD.[13]	*MRI if suggestive clinical features develop.*
Malignancy	No increased risk identified.	

Italicised points reflect personal practice rather than established recommendations.
G-CSF, granulocyte colony-stimulating factor;JCV, John Cunningham virus; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; PML, progressive multifocal leukoencephalopathy; PRES, posterior reversible encephalopathy syndrome; RA, rheumatoid arthritis.

Box 1. Approach to managing symptomatic secondary antibody deficiency

This advice is appropriate for patients satisfying all three of the following criteria:

- Maintenance rituximab therapy.
- Serious or recurrent (particularly respiratory) infections.
- Total serum IgG <6.0 g/L (recurrent infection is more likely if IgG <4.0 g/L).

Suggested management to mitigate infection risk:[89]

- Liaise with local immunology service.
- Check disease-specific circulating antibody titres against *Haemophilus influenzae* (Hib), *Clostridium tetani* and pneumococcal capsular polysaccharide.
- If titres are below protective cut-off levels (Hib >1 mcg/mL, tetanus >0.1 IU/mL, pneumococcus >50 mg/L), [90] vaccinate patients and retest titres after 6 weeks.
- Trial prophylactic antibiotic therapy.
- Immunoglobulin replacement therapy (IGRT) is justifiable if the response to test vaccination and/or antibiotics is poor.[91]
  – Initiate intravenous immunoglobulin at 0.4–0.6 g/kg/month or consider subcutaneous formulations.
  – Aim for serum IgG within normal range (6–16 g/L).
- Assess clinical response to IGRT after 6 months (burden of infections) and consider the need for long-term treatment. IGRT is unlikely to reduce the frequency of urinary tract infections.

REVIEW

Rituximab in neurological disease: principles, evidence and practice

Daniel H Whittam, [1] Emma C Tallantyre, [2,3] Stephen Jolles, [4,5] Saif Huda, [1] Robert J Moots, [6] Ho Jin Kim, [7] Neil P Robertson, [2,3] Bruce A C Cree, [8] Anu Jacob [1,9]

BMJ
Whittam DH, et al. Pract Neurol 2019;19:95–20. doi:10.1136/practneurol-2018-001899

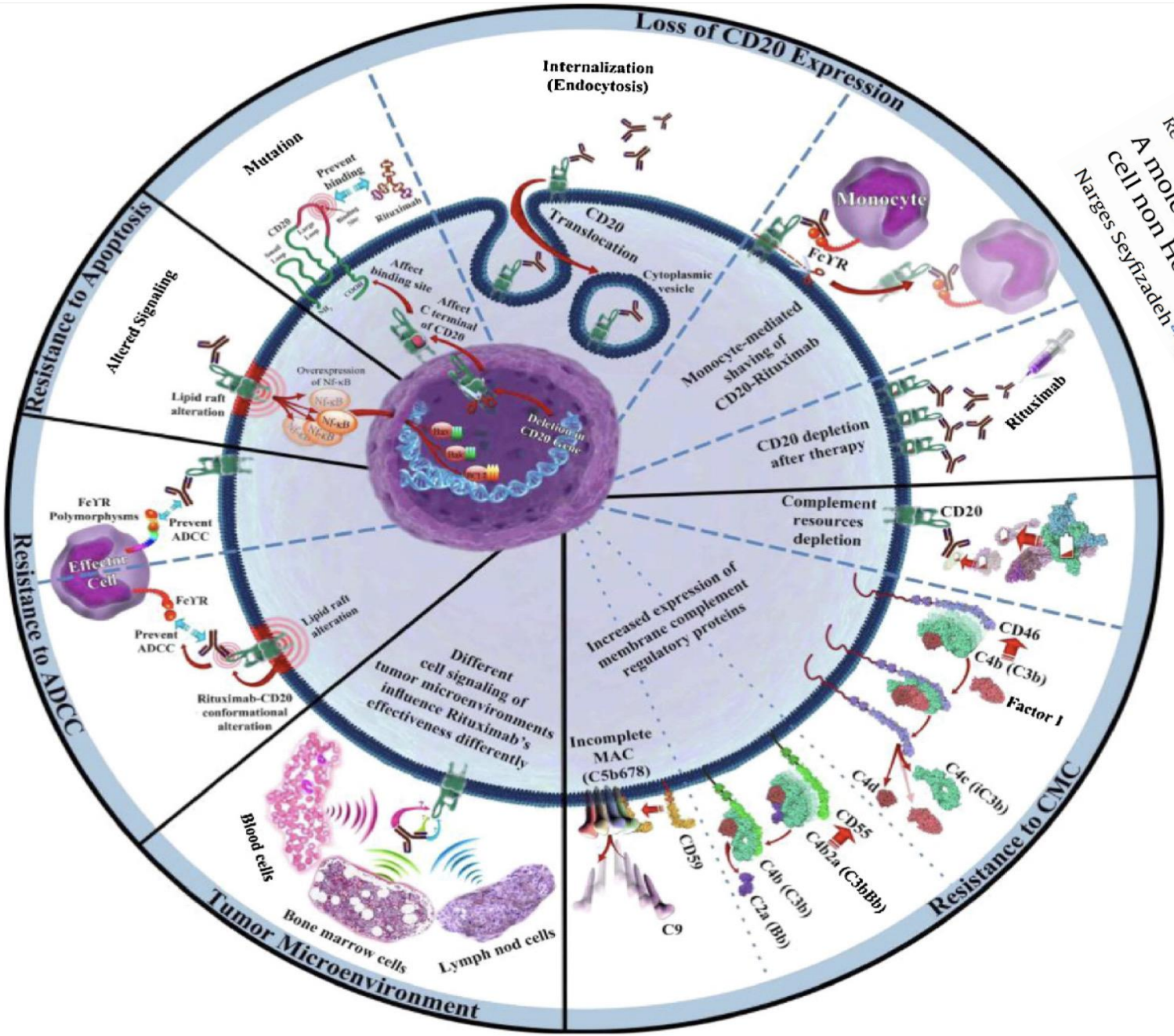

Fig. 4. Rituximab resistance mechanisms; (1) resistance to CMC, (2) resistance to ADCC, (3) resistance to apoptosis, (4) resistance due to the loss of CD20, and (5) resistance in different tumor microenvironments.

Review
A molecular perspective on rituximab: A monoclonal antibody for B cell non Hodgkin lymphoma and other affections
Critical Reviews in Oncology/Hematology
journal homepage: www.elsevier.com/locate/critrevonc
Contents lists available at ScienceDirect
Critical Reviews in Oncology/Hematology 97 (2016) 275–290

Narges Seyfizadeh [a], Nayer Seyfizadeh [b,c], Justin Hasenkamp [d], Sara Huerta-Yepez [e]

Table 1. Practice points for minimizing the risk of infectious complications during rituximab therapy

Practice points
1. Consider patient-specific risk factors prior to treatment: • Age • Indication for rituximab use • Comorbidities • Prior exposure to and concomitant use of other immunosuppression
2. Screen for HBV prior to treatment • Prophylaxis for those with positive HBV serology (as per algorithm)
3. Assess risk of TB reactivation and need for chemoprophylaxis: • Previous TB disease or exposure to TB • Interferon-gamma release assay, i.e. QuantiFERON • Chest X-ray abnormalities
4. If possible, vaccinate for bacterial and viral pathogens, including: • Pneumococcus • Influenza A and B • Haemophilus influenza B • Meningitis C • HBV
5. Prescribe prophylaxis for *Pneumocystis jiroveci* pneumonia
6. Contraceptive advice for both men and women
7. Monitor full blood count and immunoglobulins prior to and during treatment • Consider intravenous immunoglobulins if evidence of hypogammaglobulinaemia (<400 mg/dL) complicating recurrent infections
8. Remain vigilant for signs and symptoms suggestive of infection during treatment course

Table 2. Teaching points

- 20% to 40% of pMN are refractory to rituximab.
- There are 2 main mechanisms of resistance: (i) development of anti-rituximab antibodies and (ii) rituximab underdosing.
- Anti-rituximab antibodies are not uncommon. They neutralize the activity of rituximab in 80% of cases and cross-react with obinutuzumab and ofatumumab in only 20% of patients.
- Nephrotic patients quickly eliminate rituximab in the urine.
- Obinutuzumab and ofatumumab should be used in the treatment of rituximab-refractory pMN only in the presence of anti-rituximab antibodies.
- Repeated injections of rituximab should be used in the treatment of rituximab-refractory pMN only in the absence of anti-rituximab antibodies.
- Anti-rituximab antibodies might be a useful biomarker to predict clinical outcomes.

pMN, primary membranous nephropathy.

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NEPHROLOGY ROUNDS

Analysis and Management of Rituximab Resistance in PLA2R1-Associated Membranous Nephropathy

Maxime Teisseyre[1,2], Sonia Boyer-Suavet[2,3,4], Marion Crémoni[3], Vesna Brglez[2,4], Vincent Esnault[3] and Barbara Seitz-Polski[1,2,3,4]

[1]Laboratoire d'Immunologie, CHU de Nice, Université Côte d'Azur, France; [2]Centre de Référence Maladies Rares Syndrome Néphrotique Idiopathique, CHU de Nice, Université Côte d'Azur, France; [3]Service de Néphrologie-Dialyse-Transplantation, CHU de Nice, Université Côte d'Azur, France; and [4]Unité de Recherche Clinique de la Côte d'Azur (UR2CA), Université Côte d'Azur, France

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Table 2. Viral and Fungal Infections After Rituximab Therapy

Type of Viral Infection After Rituximab	n
Cytomegalovirus	5
Varicella zoster virus	3
Herpes simplex virus	1
Type of fungal infection after rituximab	
Candida albicans	4
Aspergillus fumigatus	2
Pneumocystis jirovecii	2
Cryptococcus neoformans	1

Transplantation Proceedings, 49, 2269e2273 (2017)

Incidence of Infectious Disease and Malignancies After Rituximab Therapy in Kidney Transplant Recipients: Results From a Cohort in Germany

E. Schrezenmeier[a,b,*], K. Budde[a], O. Staeck[a], L. Lehner[a], M. Duerr[a], D. Khadzhynov[a], T. Dörner[b], and F. Halleck[a]

[a]Department of Nephrology and Medical Intensive Care, Charité - Universitätsmedizin Berlin, Berlin, Germany; and [b]Department of Medicine/Rheumatology and Clinical Immunology and DRFZ, Charité Campus Mitte, Berlin, Germany

Table 3. Bacterial Infections Requiring In-Hospital Stay (n = 80) Including Causative Organisms of Bacterial Infections

Sepsis with positive blood cultures (n = 19)	*Campylobacter jejuni* (n = 1)
	Pseudomonas aeruginosa (n = 1)
	Enterococcus faecium (n = 1)
	Enterobacter cloacae (n = 1)
	Staphylococcus aureus (n = 1)
	Paenibacillus pabuli (n = 1)
	Escherichia coli (n = 8)
	E coli (ESBL positive) (n = 2)
	Klebsiella pneumoniae (n = 3)
Pneumonia (n = 10)	*Streptococcus pneumoniae* (n = 1)
	Staphylococcus epidermidis (n = 1)
	S aureus (n = 1)
	No results from culture (n = 7)
Urinary tract infection (n = 36)	*Enterococcus faecalis* (n = 6)
	E faecium (n = 3)
	E coli (n = 13)
	E coli (ESBL positive) (n = 1)
	Staphylococcus haemolyticus (n = 1)
	P aeruginosa (n = 1)
	K pneumoniae (n = 2)
	No results from urinary culture (n = 9)
Catheter-associated infection (n = 3)	*E faecalis* (n = 1)
	S epidermidis (n = 1)
	E coli (ESBL positive) (n = 1)
Erysipelas skin infection (n = 2)	No result from culture (n = 2)
Wound infection (n = 2)	*E faecium* (n = 1)
	E coli (n = 1)
Colitis (n = 4)	*Clostridium difficile* (n = 3)
	C jejuni (n = 1)
Otitis (n = 2)	*K pneumoniae* (n = 2)
Sakroileitis (n = 1)	*S aureus* (n = 1)
Atypical mycobacteriosis (n = 1)	*Mycobacterium kansasii* (n = 1)

Abbreviations: ESBL, extended-spectrum beta-lactamases.

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[a]Department of Nephrology and Medical Intensive Care, Charité - Universitätsmedizin Berlin, Berlin, Germany; and [b]Department of Medicine/Rheumatology and Clinical Immunology and DRFZ, Charité Campus Mitte, Berlin, Germany

RHEUMATOLOGY

Rheumatology 2021;60:3496–3502
doi:10.1093/rheumatology/keab223
Advance Access publication 12 March 2021

Review

COVID-19 vaccination and antirheumatic therapy

Jack Arnold[1], Kevin Winthrop[2] and Paul Emery [1,3]

Abstract

The coronavirus disease 2019 (COVID-19) vaccination will be the largest vaccination programme in the history of the NHS. Patients on immunosuppressive therapy will be among the earliest to be vaccinated. Some evidence indicates immunosuppressive therapy inhibits humoral response to the influenza, pneumococcal and hepatitis B vaccines. The degree to which this will translate to impaired COVID-19 vaccine responses is unclear. Other evidence suggests withholding MTX for 2 weeks post-vaccination may improve responses. Rituximab has been shown to impair humoral responses for 6 months or longer post-administration. Decisions on withholding or interrupting immunosuppressive therapy around COVID-19 vaccination will need to be made prior to the availability of data on specific COVID-19 vaccine response in these patients. With this in mind, this article outlines the existing data on the effect of antirheumatic therapy on vaccine responses in patients with inflammatory arthritis and formulates a possible pragmatic management strategy for COVID-19 vaccination.

Key words: COVID-19, vaccine, biologics, DMARDs, rituximab, methotrexate

TABLE 2 Summary of the evidence for the effect of common DMARDs/biologic therapies on vaccine response

Drug	Findings	Interpretation/advice on management
Corticosteroids	• Doses >10 mg prednisolone daily associated with impaired humoral immunity [1–5]. • Doses <10 mg prednisolone daily not shown to impair humoral response. • Doses >10 mg prednisolone daily associated with poorer outcomes in hospitalized COVID-19 patients [6].	• Channelling bias present, as patients on steroid therapy generally sicker. • Could consider tapering prednisolone to <10 mg daily where possible, likely already standard practice.
csDMARDs (not MTX)	• Small reduction in vaccine-induced antibody levels but maintained seroprotective titres [7–11].	• Continue therapy.
Anti-CD20	• Shown to impair humoral response to both PPSV-23 and influenza vaccine [3, 12, 27, 28]. • Effect most pronounced if vaccinated earlier <3 months after rituximab therapy [27, 28]. • Improved vaccine response if vaccinated >6 months after RTX therapy [27, 28].	• Aim to vaccinate before RTX or >6 months post-RTX treatment where possible. • Could consider postponed therapy in specific cases.

csDMARD: conventional synthetic DMARD; JAK: Janus kinase; PCV-7: heptavalent pneumococcal conjugate vaccine; PCV-13: 13 valent pneumococcal conjugate vaccine; PPSV-23: pneumococcal polysaccharide vaccine; RTX: Rituximab; S/C: Subcutaneous injection.

zoster vaccine, starting tofacitinib 2–3 weeks post-vaccination yielded similar humoral and cell-mediated responses to controls [26].

Anti-CD20

- Shown to impair humoral response to both PPSV-23 and influenza vaccine [3, 12, 27, 28].
- Effect most pronounced if vaccinated earlier <3 months after rituximab therapy [27, 28].
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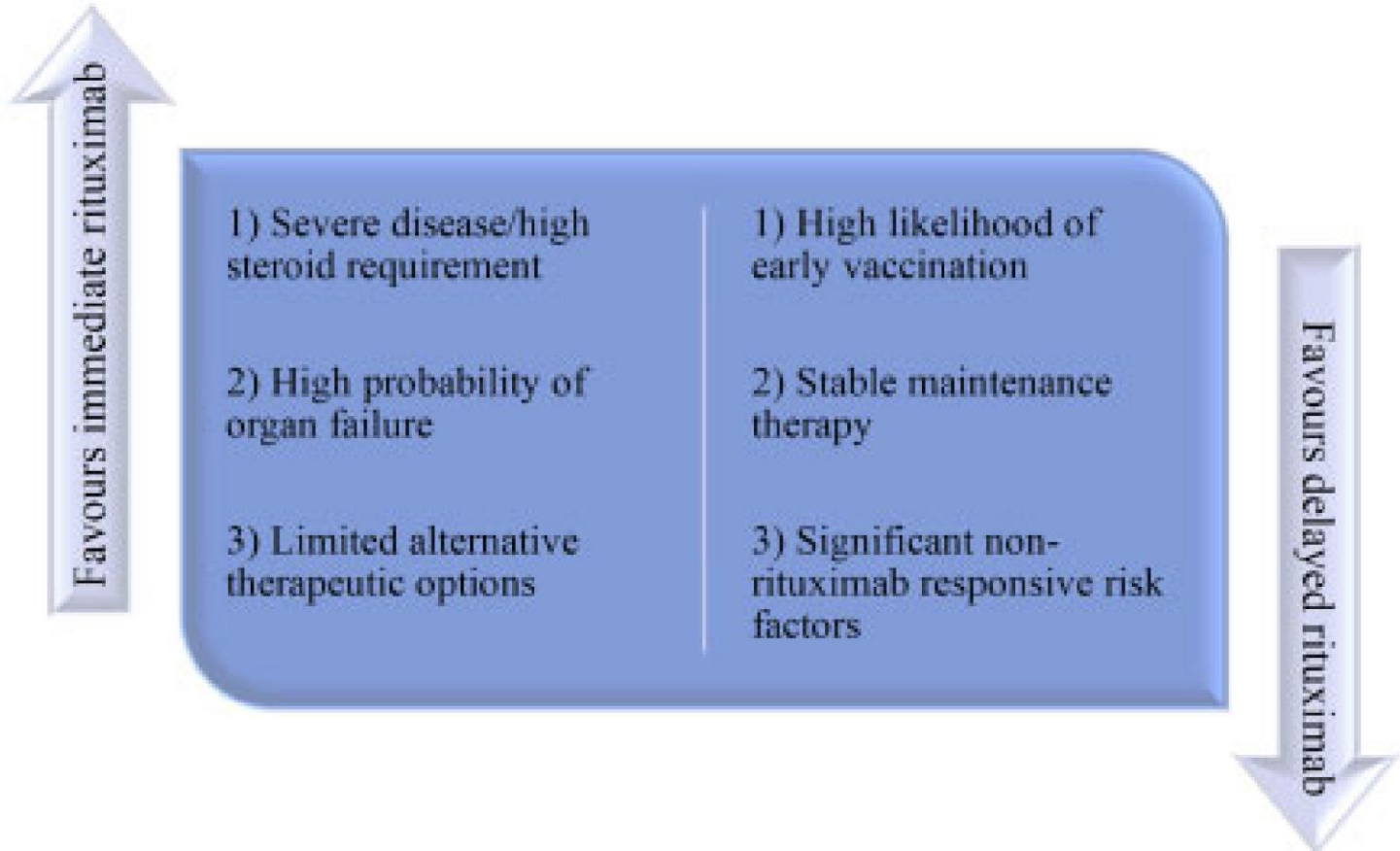
RHEUMATOLOGY

Review

COVID-19 vaccination and antirheumatic therapy

Jack Arnold[1], Kevin Winthrop[2] and Paul Emery[1,3]

FIG. 1 Factors influencing rituximab treatment decisions



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RHEUMATOLOGY
Review

COVID-19 vaccination and antirheumatic therapy

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KEY POINTS

- Immune responses mediated by B cells (which produce antibodies and cytokines and present antigen to T cells) are important in autoimmune renal disease and transplantation
- B-cell depletion can alter the course of autoimmune and alloimmune responses
- Monoclonal antibodies to B-cell antigens can effectively deplete circulating B cells, diminishing their effector functions
- Rituximab, a monoclonal antibody directed against CD20, has been successfully used in hematological B-cell disorders
- Rituximab has been used in a number of autoimmune conditions and in transplantation with some success
- Randomized trials are required to compare the short-term and long-term efficacy of B-cell deletional strategies with conventional immuno-suppressants in the treatment of renal disease

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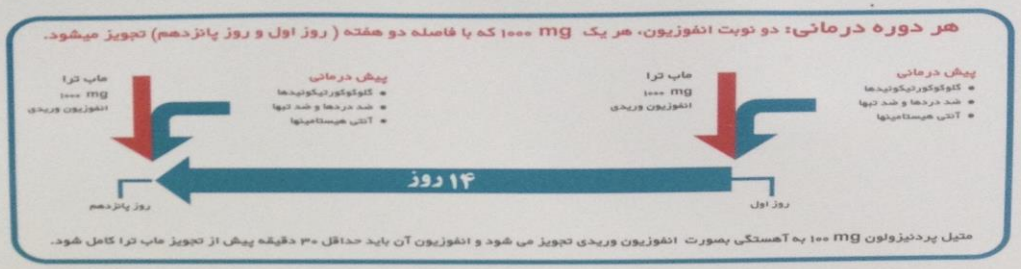

متیل پردنیزولون ۱۰۰ mg به آهستگی بصورت انفوزیون وریدی تجویز می شود و انفوزیون آن باید حداقل ۳۰ دقیقه پیش از تجویز ماب ترا کامل شود.

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به آرامی به پایین و بالا برگردانید تا مخلوط شود

از ایجاد کف اجتناب کنید

پیش درمانی

محلول انفوزیون آماده شده برای ۲۴ ساعت در دمای ۲–۸° C و ۱۲ ساعت در دمای اتاق قابل نگهداری است

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انفوزیون اول ۵۰ mg در ساعت

سرعت اولیه انفوزیون ۵۰ mg/h

۱۰۰ mg/h → ۱۵۰ mg/h → ۲۰۰ mg/h → ۲۵۰ mg/h → ۳۰۰ mg/h → ۳۵۰ mg/h → ۴۰۰ mg/h

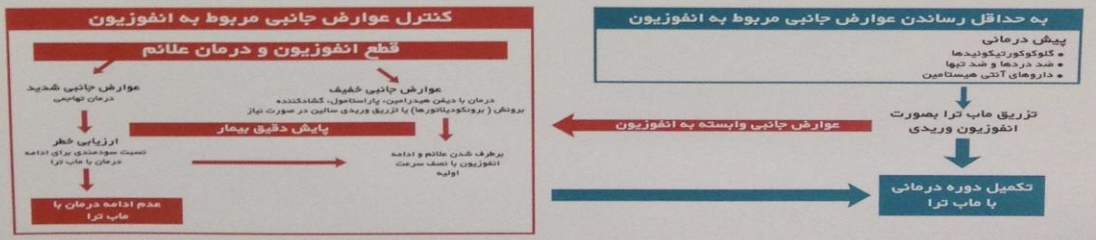
مدت زمان معمول جهت انفوزیون اول ۴ ساعت و ۱۵ دقیقه است. سرعت اولیه ۵۰ mg/h است که هر ۳۰ دقیقه یکبار ۵۰ mg/h به آن اضافه می شود تا حداکثر به ۴۰۰ mg/h برسد.

انفوزیون بعدی ۱۰۰ mg در ساعت

۱۰۰ mg/h → ۲۰۰ mg/h → ۳۰۰ mg/h → ۴۰۰ mg/h

مدت زمان معمول جهت انفوزیون دوم ۳ ساعت و ۱۵ دقیقه است. سرعت اولیه ۱۰۰ mg/h است که هر ۳۰ دقیقه یکبار ۱۰۰ mg/h به آن اضافه می شود تا حداکثر به ۴۰۰ mg/h برسد.

کنترل واکنشهای حین انفوزیون



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