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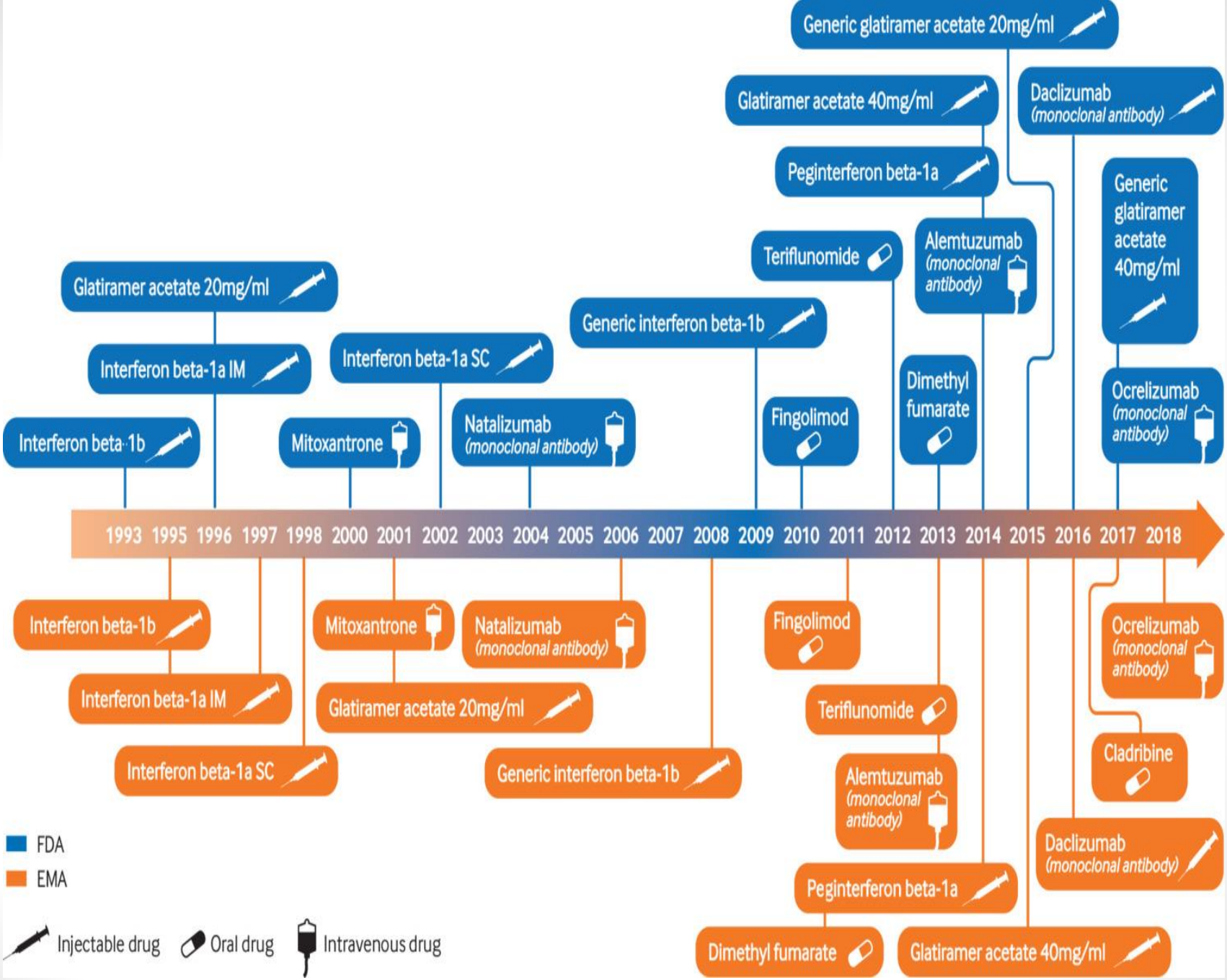
- Multiple sclerosis, the prototypical inflammatory demyelinating disease of the central nervous system, is second only to trauma as a cause of acquired neurologic disability in young adults.[1]

- In contrast to earlier concepts of disease suggesting that pathogenic T cells are sufficient for full expression of multiple sclerosis, it is now evident that autoimmune B cells and humoral immune mechanisms also play key roles.

- Therapies (e.g., interferon beta and glatiramer acetate) developed on the basis of this theory decrease the relapse rate by approximately one third[3,4]


Generic glatiramer acetate 20mg/ml
Glatiramer acetate 40mg/ml
Daclizumab (monoclonal antibody)
Peginterferon beta-1a
Generic glatiramer acetate 40mg/ml
Teriflunomide
Alemtuzumab (monoclonal antibody)
Glatiramer acetate 20mg/ml
Generic interferon beta-1b
Interferon beta-1a IM
Interferon beta-1a SC
Dimethyl fumarate
Ocrelizumab (monoclonal antibody)
Interferon beta-1b
Mitoxantrone
Natalizumab (monoclonal antibody)
Fingolimod
1993 1995 1996 1997 1998 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018
Interferon beta-1b
Mitoxantrone
Natalizumab (monoclonal antibody)
Fingolimod
Ocrelizumab (monoclonal antibody)
Interferon beta-1a IM
Glatiramer acetate 20mg/ml
Teriflunomide
Cladribine
Interferon beta-1a SC
Generic interferon beta-1b
Alemtuzumab (monoclonal antibody)
Daclizumab (monoclonal antibody)
Peginterferon beta-1a
FDA
EMA
Dimethyl fumarate
Glatiramer acetate 40mg/ml
Injectable drug
Oral drug
Intravenous drug

-High anti-EBV titers and a history of IM increase the risk of MS

-Vitamin D regulates expression of genes involved in B cell differentiation and activation

-Peripheral B cells show higher expression of the α4 subunit of the VLA-4 receptor

-CSF B cell counts are increased

-Markers of B cell activation (OCB, CXCL13, MRZ reaction) predict conversion to RRMS

-The presence of OCB is found in more than 95% of MS cases

-OCB production is significantly associated with the *HLA-DRB1*1501* allele

-The presence of OCB influences MRI features and disease progression

-More than 99.5% of MS patients are EBV+

-CSF CXCL13 levels correlate with CSF total leukocytes and B cells counts, markers of demyelination and blood brain barrier leakage, MRI activity and relapses

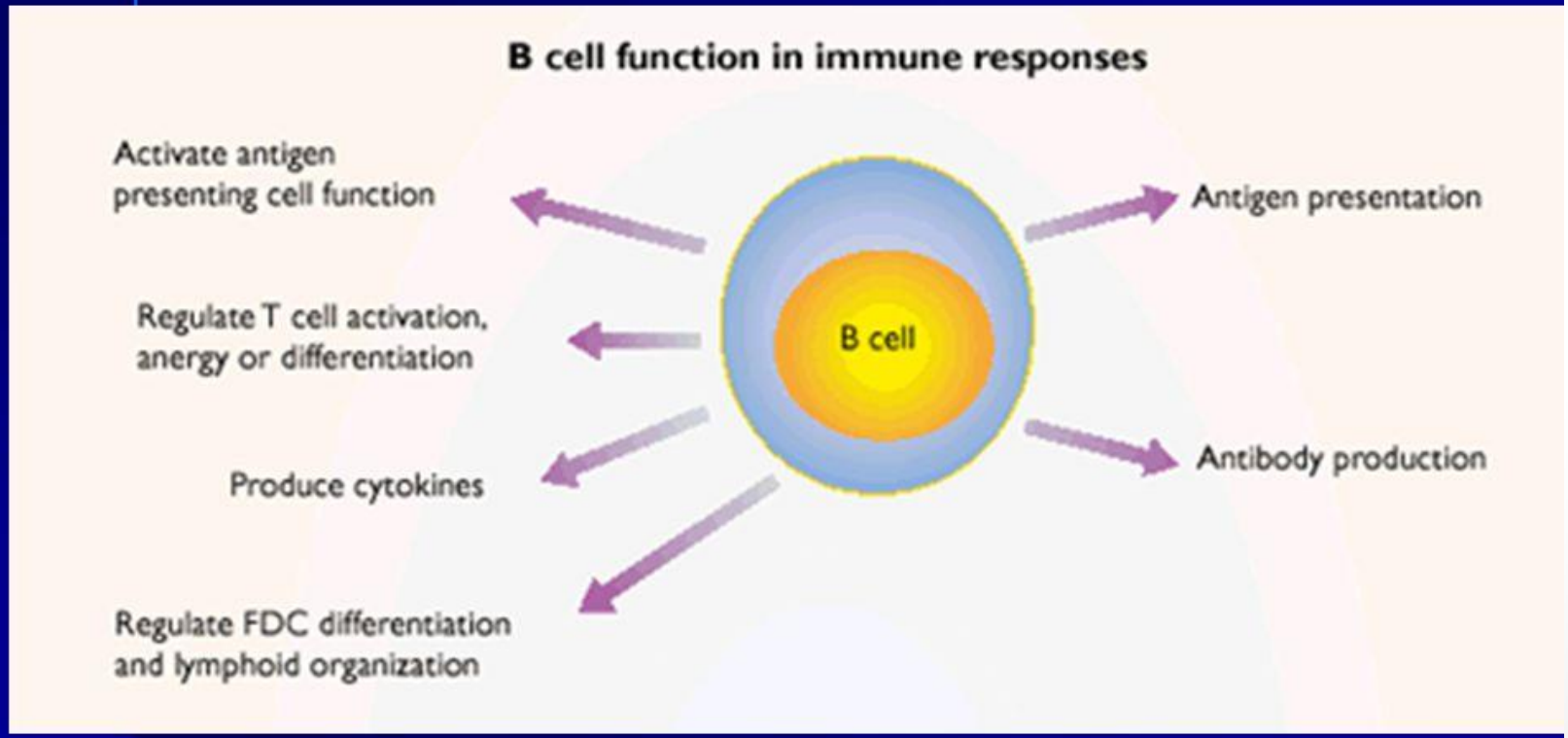
-B cell depletion reduces the number of new Gd enhancing lesions, relapses, CSF T cell counts and T cell proliferation and activation

-B cell GC like structures are found in the meninges of SPMS cases and associate with earlier age at onset, age at use of wheelchair, age at death, grey matter demyelination and gradient of cortical -neuronal loss

-Some evidence for presence of EBV in B and plasma cells infiltrating MS brain and meninges (also seen in RRMS and PPMS)

B CELL INVOLVEMENT

B-cell Functions



If the BCR binds to a pathogens (bacterial cell in the diagram), the BCR receptor becomes cross-linked which induces intracellular signaling in the B cells. This is the first step in B cell activation.

This primarily occurs in local lymph nodes near the site of infection. The pathogens get to the lymph nodes via lymph.

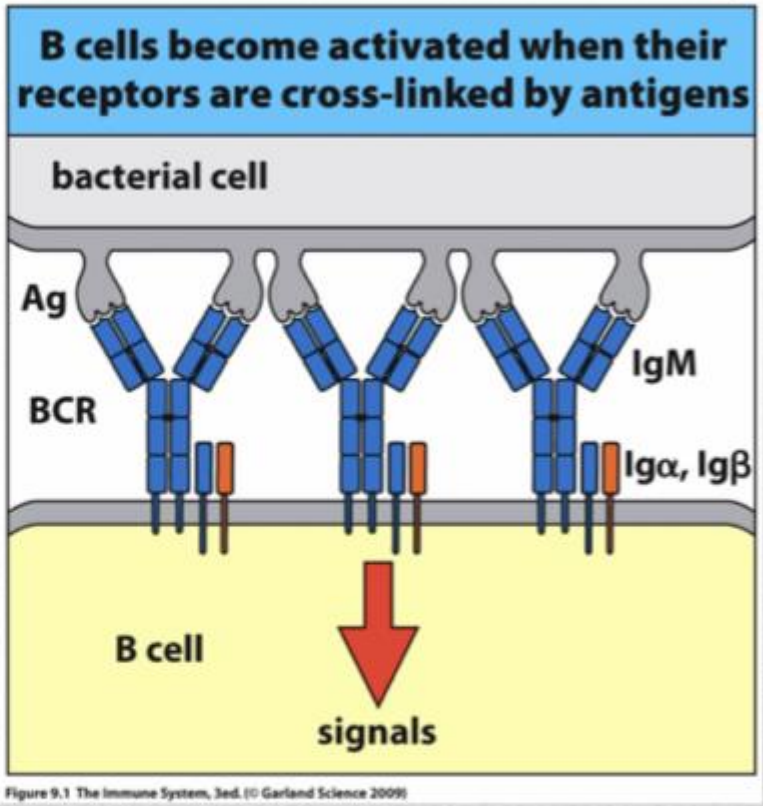
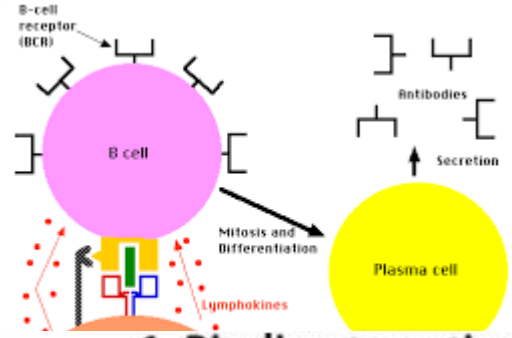
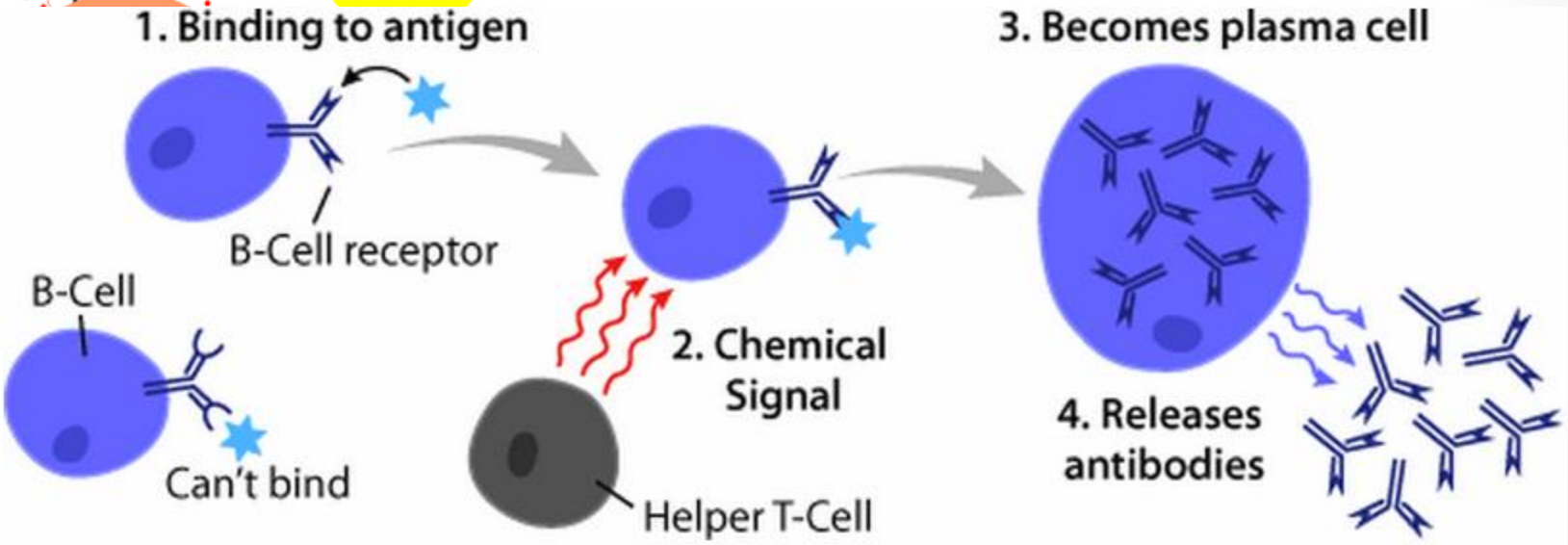


Figure 9.1 The Immune System, 3ed. (© Garland Science 2009)

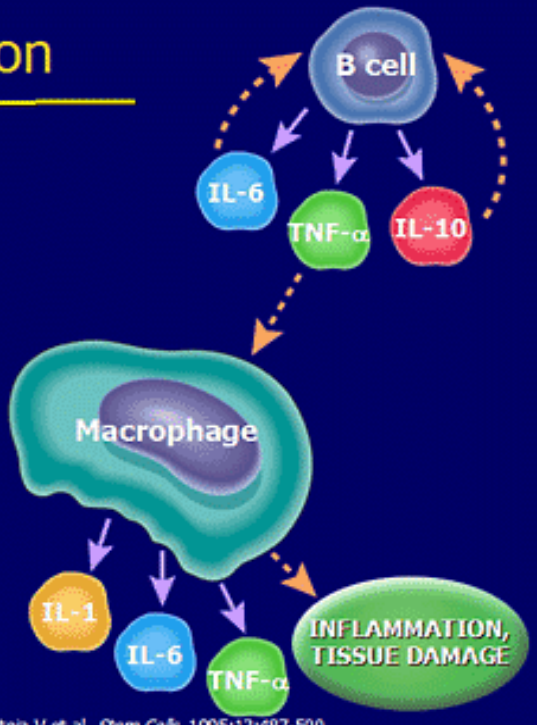
B Cell Activation


B-cell receptor (BCR)
B cell
Antibodies
Secretion
Mitosis and Differentiation
Plasma cell
Lymphokines


1. Binding to antigen
3. Becomes plasma cell
B-Cell receptor
B-Cell
Can't bind
2. Chemical Signal
Helper T-Cell
4. Releases antibodies

Cytokine Production

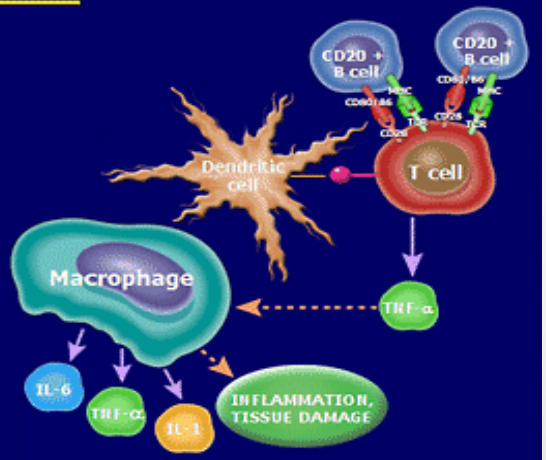
- B cells can produce proinflammatory cytokines
  - TNF-α; IL-1
- B cells can also produce cytokines with autocrine/ stimulatory effects
  - IL-6; IL-10



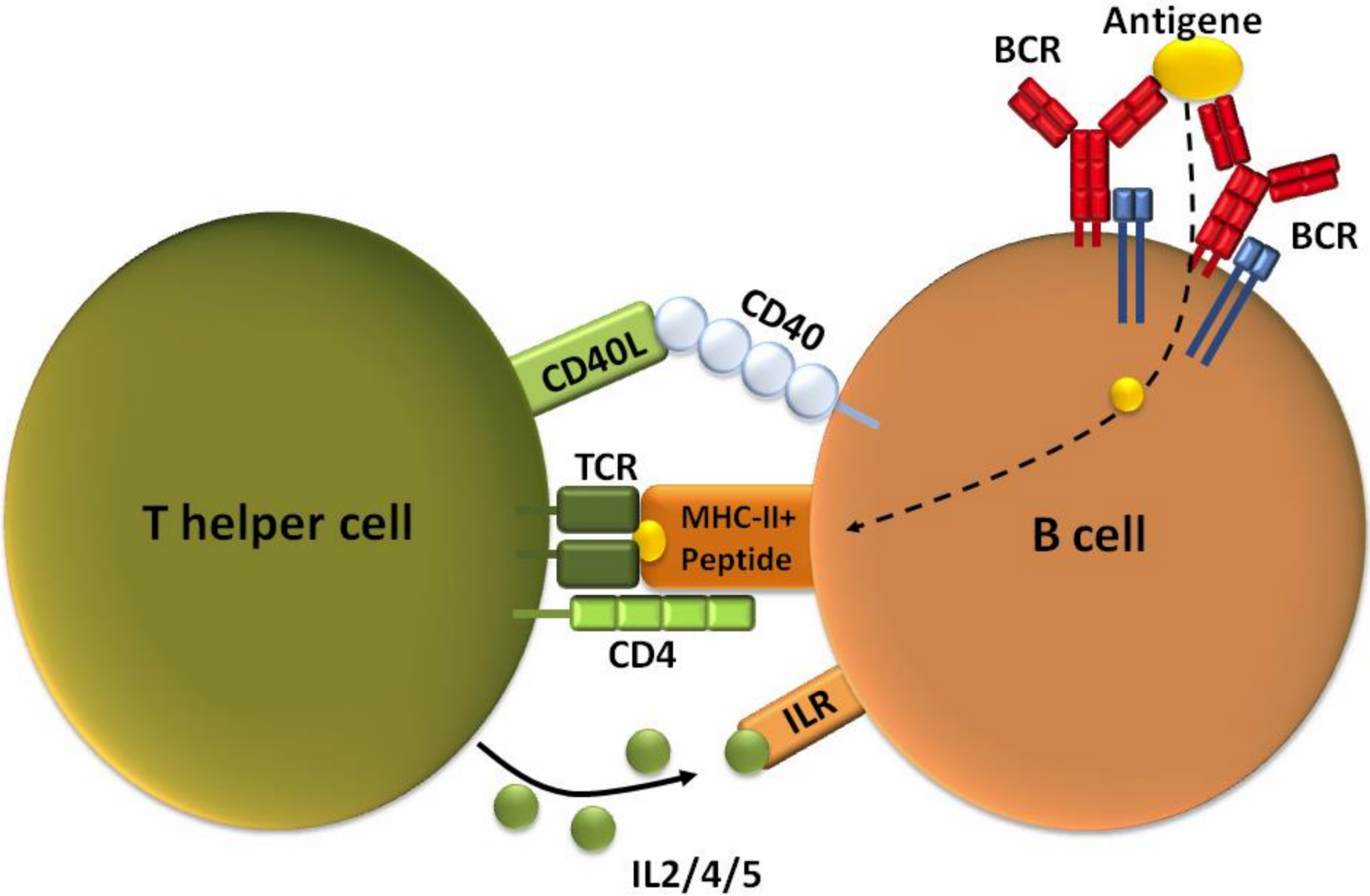
Takemura S et al. *J Immunol.* 2001;167:4710-4718; Pistoia V et al. *Stem Cells.* 1995;13:487-500.

The Role of B Cells in T-Cell Activation

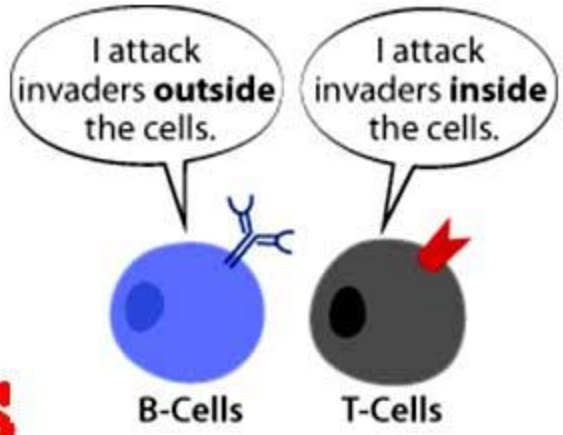
- Activated B cells
  - Direct T-cell activation
  - Direct subsequent T-cell activation of macrophages
- B cells act as APCs



Takemura S et al. *J Immunol.* 2001;167:4710-4718; Alberts B et al. *Molecular Biology of the Cell.* 3rd ed. New York, NY: Garland Publishing; 1994; Metlay JP et al. *Adv Immunol.* 1989;47:45-116.


Antigene
BCR
BCR
CD40L
CD40
TCR
T helper cell
MHC-II+
Peptide
B cell
CD4
ILR
IL2/4/5

Differences Between B-Cells and T-Cells



Some of the differences between B Cells and T Cells are as follows:

S.N.	Properties	**B-Cells**	**T-Cells**
1	**Name**	B lymphocytes	T lymphocytes
2	**Origin**	Bone Marrow	Thymus
3	**Position**	Outside Lymph Node	Interior of Lymph Node
4	**Membrane receptor**	BCR (= immunoglobulin) for antigen	TCR for antigen
5	**Connections**	B-cells can connect to antigens right on the surface of the invading virus or bacteria.	T-cells can only connect to virus antigens on the outside of infected cells.

6	**Tissue Distribution**	Germinal centres of lymph nodes, spleen, gut, respiratory tract; also subcapsular and medullary cords of lymph nodes	Parafollicular areas of cortex in nodes, periarteriolar in spleen
7	**Life Span**	Life span is short	Life span is long
8	**Surface Antibodies**	Surface Antibodies present	Absence of surface antibodies
9	**Secretion**	They secrete antibodies	They secrete Lymphokines
10	**Function**	B-cells form humoral or antibody-mediated immune system (AMI).	T-cells form cell-mediated immune system (CMI).
11	**Blood**	20% of lymphocytes	80% of lymphocytes; CD4 > CD8

12	**Formation**	They form plasma cells and memory cells.	They form killer, helper and suppressor cells.
13	**Movement to Infection Site**	Plasma cells do not move to the site of infection.	Lymphoblasts move to the site of infection.
14	**Function**	Plasma cells do not react against transplants and cancer cells.	Killer cells react against transplants and cancer cells.
15	**Function**	Plasma cells have no inhibitory effect on immune system.	Suppressor cells inhibit immune system.
16	**Function**	They defend against viruses and bacteria that enter the blood and lymph.	They defend against pathogens including protists and fungi that enter the cells.

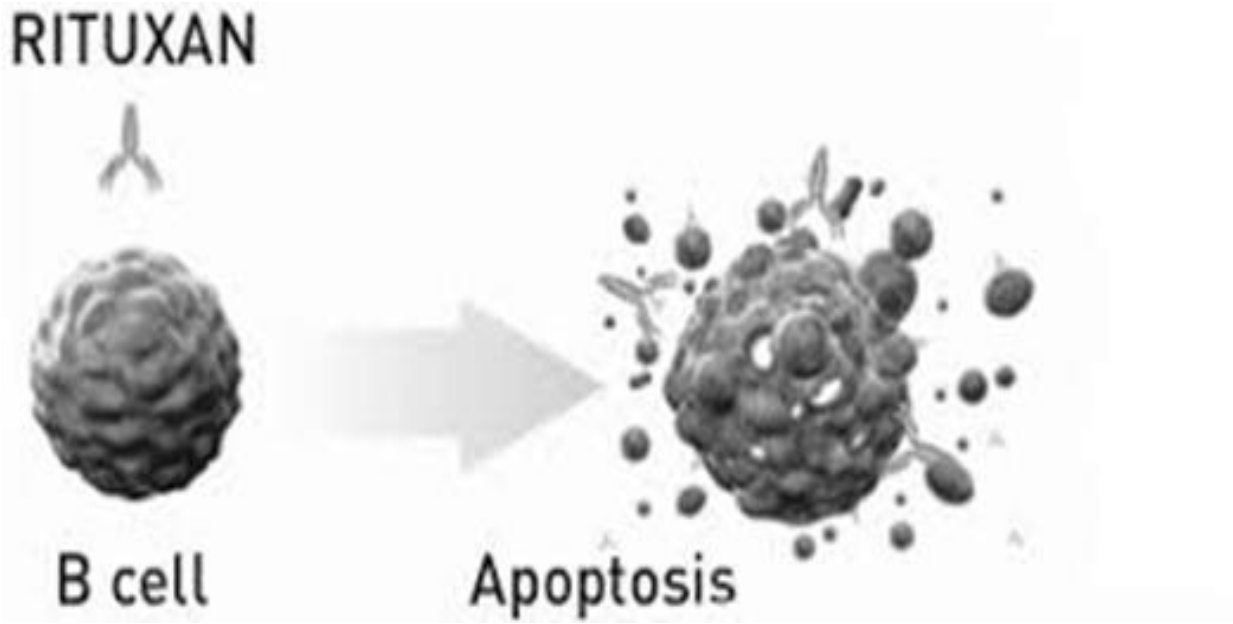
- **Rituximab** is a monoclonal antibody against the protein CD20, which is primarily found on the surface of immune system B cells.

- Rituximab destroys B cells and is therefore used to treat diseases which are characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells.Rituximab

- RTX is approved for non Hodgkin lymphoma and rheumatoid arthritis for example but is prescribed by some neurologists for multiple sclerosis (MS) based upon clinical trials that showed efficacy as a disease modifying therapy (DMT).

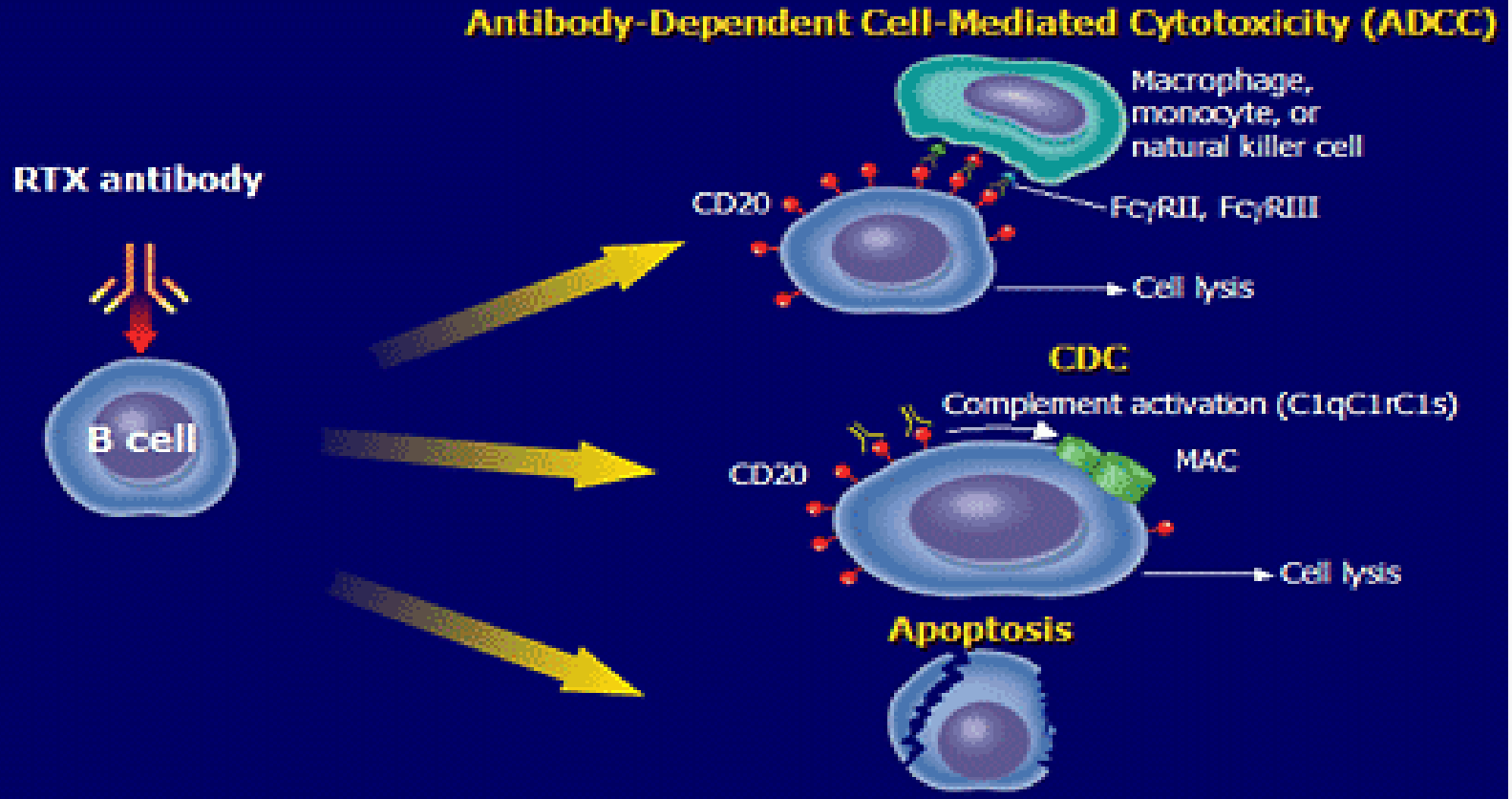
Mechanism of action of rituximab

- Rituximab : is a genetically engineered chimeric monoclonal antibody that depletes CD20+ B cells through a combination of cell-mediated and complement-dependent cytotoxic effects and the promotion of apoptosis.[24-26]

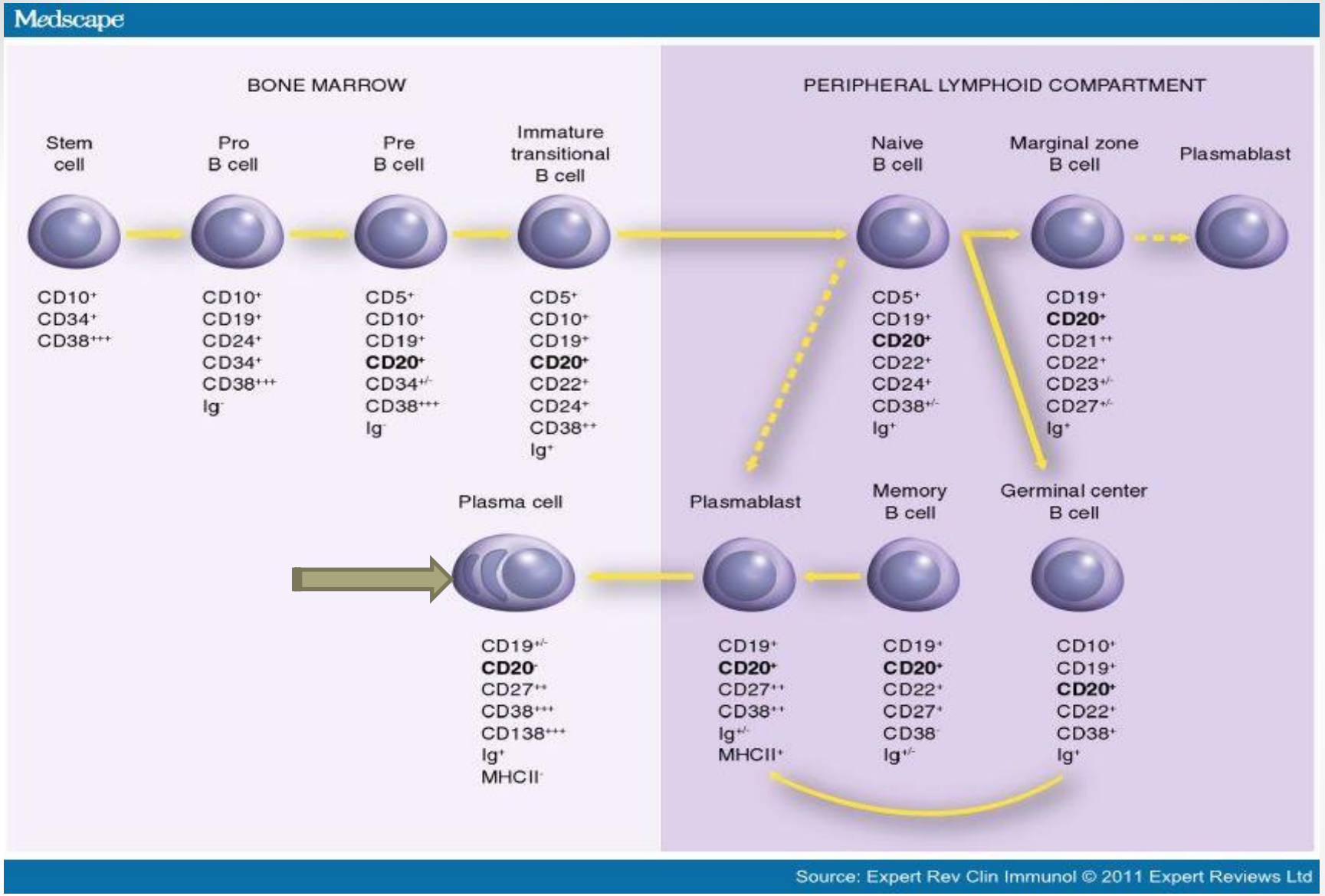


- B-cell depletion affects antibody production, cytokine networks, and B-cell–mediated antigen presentation and activation of T cells and macrophages.

Rituximab: Mechanism of Action



Anderson DR et al. *Biochem Soc Trans.* 1997;25:705-708; Golay J et al. *Blood.* 2000;95:3900-3908; Reff ME et al. *Blood.* 1994;83:435-445; Clynes RA et al. *Nat Med.* 2000;6:443-446; Shan D et al. *Cancer Immunol Immunother.* 2000;48:673-683; Silverman GJ et al. *Arthritis Rheum.* 2003;48:1484-1492.



- Plasma cells are not targeted by rituximab, and total antibody levels were not significantly reduced after a single treatment course; thus, the rapid onset of action is unlikely to be explained by a reduction in pathogenic autoantibodies

- Effects of rituximab on MRI and clinical outcomes seen resulted from lysis of memory B cells located in the peripheral blood and lymphoid tissues, or perhaps in the central nervous system. Interference with antigen presentation by B cells, or with activation of T cells or macrophages by pro-inflammatory B-cell cytokines such as interferon-γ and interleukin-12, may also play a role.[32]

- B-cell depletion has the potential to decrease disease activity in patients with the relapsing form of this disease.

- Rituximab:, has shown beneficial effects in 2 randomized placebo-controlled phase 2 trials (RCTs):
- **RTX in Adults With Primary Progressive Multiple Sclerosis (OLYMPUS)**

- **Rituximab in primary progressive MS**
- Results of a phase 2/3 trial (OLYMPUS) were published in 2009. Ritixumib did not slow disability progression compared with placebo. But researchers reported that rituximab might be effective in younger people and those with active inflammation.

- **RTX in Relapsing-Remitting Multiple Sclerosis (HERMES)**

- Since the publication of the HERMES[1] and OLYMPUS[2] trials, rituximab has been increasingly used off-label to treat MS in Sweden, in progressive MS with signs of disease activity, and in JCV-positive RRMS with active disease course.

ARTICLES

Rituximab in multiple sclerosis

A retrospective observational study on safety and efficacy

OPEN

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Rasmus Svenningsson
Peter Alping
Lenka Novakova, MD
Anna Björck, MD
Katharina Fink, MD
Protik Islam-Jakobsson, MD
Clas Malmeström, MD, PhD
Markus Axelsson, MD, PhD
Mattias Vågberg, MD
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Jan Lycke, MD, PhD
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Correspondence to Dr. Salzer: jonatan.salzer@umu.se

ABSTRACT

Objective: To investigate the safety and efficacy of rituximab in multiple sclerosis (MS).

Methods: In this retrospective uncontrolled observational multicenter study, off-label rituximab-treated patients with MS were identified through the Swedish MS register. Outcome data were collected from the MS register and medical charts. Adverse events (AEs) grades 2-5 according to the Common Terminology Criteria for Adverse Events were recorded.

Results: A total of 822 rituximab-treated patients with MS were identified: 557 relapsing-remitting MS (RRMS), 198 secondary progressive MS (SPMS), and 67 primary progressive MS (PPMS). At baseline, 26.2% had contrast-enhancing lesions (CELs). Patients were treated with 500 or 1,000 mg rituximab IV every 6-12 months, during a mean 21.8 (SD 14.3) months. During treatment, the annualized relapse rates were 0.044 (RRMS), 0.038 (SPMS), and 0.015 (PPMS), and 4.6% of patients displayed CELs. Median Expanded Disability Status Scale remained unchanged in RRMS ($p = 0.42$) and increased by 0.5 and 1.0 in SPMS and PPMS, respectively ($p = 0.10$ and 0.25). Infusion-related AEs occurred during 7.8% of infusions and most were mild. A total of 89 AEs grades ≥2 (of which 76 infections) were recorded in 72 patients. No case of progressive multifocal leukoencephalopathy was detected.

Conclusions: This is the largest cohort of patients with MS treated with rituximab reported so far. The safety, clinical, and MRI findings in this heterogeneous real-world cohort treated with different doses of rituximab were similar to those reported in previous randomized controlled trials on B-cell depletion therapy in MS.

Classification of evidence: This study provides Class IV evidence that for patients with MS, rituximab is safe and effective. *Neurology*® 2016;87:2074-2081

- To investigate the safety and efficacy of rituximab in multiple sclerosis (MS).
- A total of 822 rituximab-treated patients with MS were identified: 557 relapsing-remitting MS (RRMS), 198 secondary progressive MS (SPMS), and 67 primary progressive MS (PPMS).
- Patients were treated with 500 or 1,000 mg rituximab IV every 6–12 months, during a mean 21.8 (SD 14.3) months
- During treatment, the annualized relapse rates were 0.044 (RRMS), 0.038 (SPMS), and 0.015 (PPMS), and 4.6% of patients displayed CELs.
- Median Expanded Disability Status Scale remained unchanged in RRMS (p = 0.42) and increased by 0.5 and 1.0 in SPMS and PPMS, respectively

- **Conclusions:**
- **This is the largest cohort of patients with MS treated with rituximab reported so far.** The safety, clinical, and MRI findings in this heterogeneous real-world cohort treated with different doses of rituximab were similar to those reported in previous randomized controlled trials on B-cell depletion therapy in MS.
- **Classification of evidence:**
- This study provides Class IV evidence that for patients with MS, **rituximab is safe and effective.**

RESEARCH ARTICLE

Effectiveness and safety of Rituximab in multiple sclerosis: an observational study from Southern Switzerland

Barbara Scotti[1], Giulio Disanto[2], Rosaria Sacco[2], Marilu' Guigli[3], Chiara Zecca[2☯], Claudio Gobbi[1,2☯*]

1 University Hospital Basel, University of Basel, Basel, Switzerland, **2** Neurocentre of Southern Switzerland, Ospedale Civico, Lugano, Switzerland, **3** Università della Svizzera Italiana (USI), Facoltà di scienze biomediche, Lugano, Switzerland

☯ These authors contributed
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Results

Out of 453 MS patients, 82 were treated with RTX, 43 (52.4%) relapsing-remitting (RRMS) and 39 (47.6%) progressive MS (median age = 48 [40–54] years, females n = 60 [73.2%], EDSS = 4.0 [2.5–6.0], median follow-up = 1.5 [1.0–2.5] years). Three relapses occurred and 59 (75.6%) patients had not EDA at follow-up end. Time to EDA was similar in RTX and natalizumab treated RRMS patients (HR = 1.64, 95%CI = 0.46–5.85, p = 0.44). Twenty-four patients presented non infusion related adverse events (infections), requiring RTX discontinuation in 6 individuals.

Effectiveness of RTX compared to NTZ in RRMS

There was no significant difference between RRMS patients under RTX and those under NTZ in
Terms of time to EDA after correction for age, sex, baseline EDSS, NT2 lesions at baseline scan

- Encouraging positive results on effectiveness of B-cell-depleting therapies are increasingly perceived as an important addition to the existing panel of DMT in MS.

- In this study including RRMS and PMS followed for a median time of 1.5 years, almost 80% of the patients had not EDA, with no difference between RRMS and PMS.

- Effectiveness did not appear to be influenced by demographic and clinical characteristics at baseline, including EDSS and number of clinical relapses in the two years preceding RTX initiation, suggesting that most patients can benefit from such treatment.

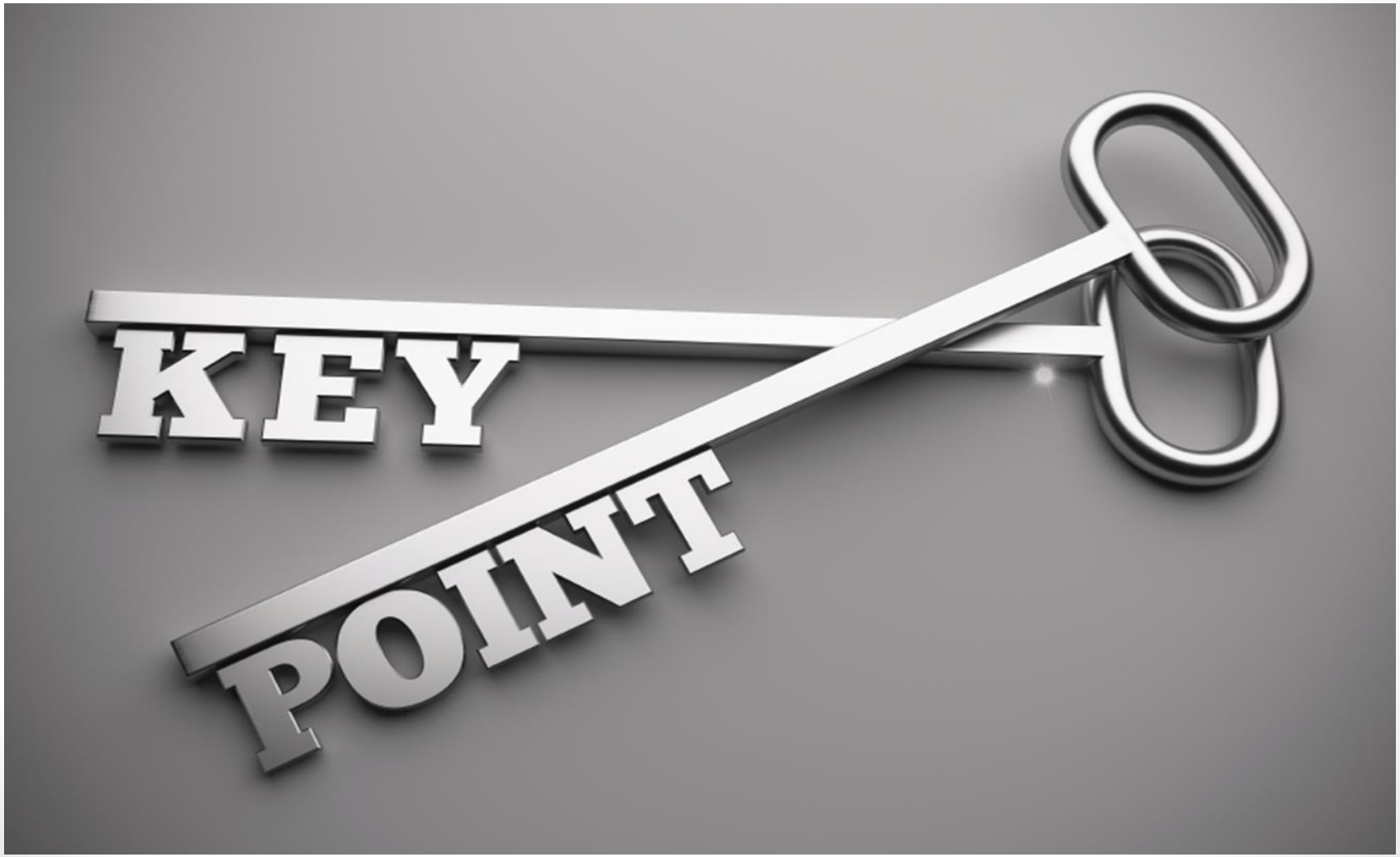
- Only three patients experienced minor relapses and all of them had PMS

- no relapses occurred in the MS patients who were switched from NTZ to RTX because of positive JCV serology.

- Within RRMS patients, disease activity was similarly reduced in RTX vs NTZ treated individuals

- As expected, there was a striking and stable reduction of CD19+ B cell concentration after RTX initiation, while CD4+ and CD8+ levels did not appear considerably influenced by RTX treatment.

What are the valuable and key points about this drug?



- The reduction in inflammatory lesions occurred at the earliest time point measured — within 4 weeks after the first dose

- Infusion-related AEs occurred during 7.8% of infusions and most were mild .In addition, infusion-related AEs were most common during the first 1 3 infusions, indicating that the potential immunogenicity of rituximab is a minor clinical problem.

- No case of progressive multifocal leukoencephalopathy was detected. In one study detected no cases of PML, despite the fact that 83.3% were seropositive among those with known JCV sero status

- RTX is effective in RRMS with a discontinuation rate that is lower than that of other DMT

- higher efficacy of RTX when administered in the earliest stages of disease when the inflammatory component is prominent

- rituximab treated patients with RRMS may be expected to experience one relapse every 23rd year

- Most of the CELs that were detected appeared early (within months) after rituximab initiation, suggesting lingering disease activity, which eventually disappeared

- This is low compared with first-line-agent treated patients with MS,and even compared with alemtuzumab- and natalizumab-treated patients.

- NTZ treatment is known to be associated with a potential risk of disease rebound following its discontinuation, particularly in highly active patients [6,15]. As previously suggested, these findings indicate that RTX may represent a valid treatment option also in this context

- rituximab is superior to fingolimod regarding disease reactivation in patients switching from natalizumab due to positive JC virus
- (JCV) serology.

Natalizumab: Switching (cont)

- Retrospective chart review of patients switching from natalizumab to
  - DMF (n = 110)
  - Fingolimod (n = 50)
  - Rituximab (n = 69)
- Median transition time
  - Natalizumab → DMF = 0 mo
  - Natalizumab → rituximab, fingolimod = 1 mo
- Discontinuation rate
  - → DMF = 24%
  - → Fingolimod = 17%
  - → Rituximab = 0%
- Percentage with enhancing lesions
  - DMF = 6.0%
  - Fingolimod = 9.1%
  - Rituximab = 0%

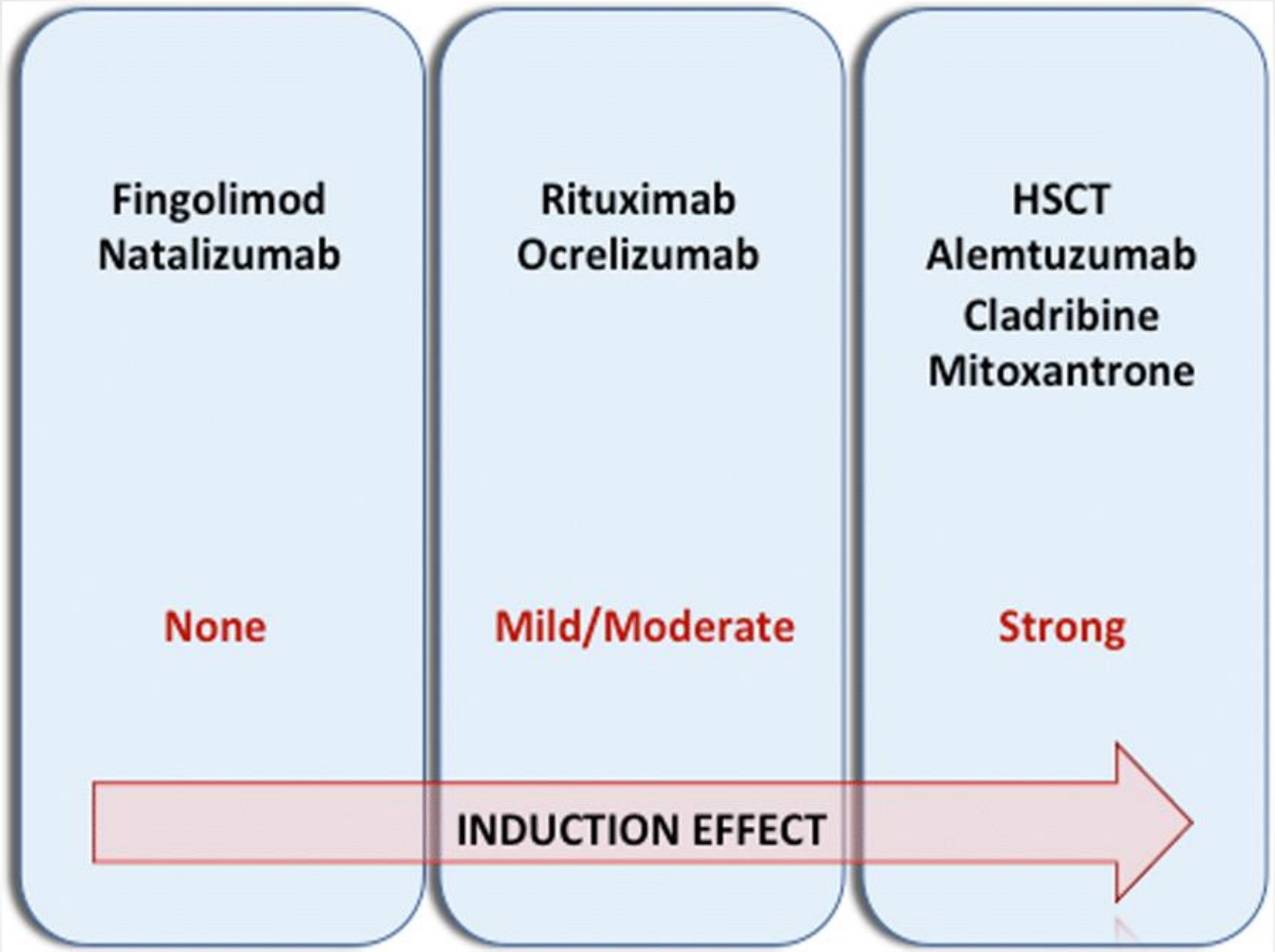
Alvarez E, et al. AAN 2015. Presentation P3.288.[9]

- The recent study by Granqvist et al. reporting a **superior effectiveness of RTX compared to injectable DMTs and dimethyl fumarate,** and a trend towards **a lower relapse rate as compared to NTZ and fingolimod in newly diagnosed RRMS**

- no serious concern for increased risk of cancer has arisen from RTX use in different clinical indications for almost two decades

- infections were more frequent in progressive patients, suggesting RTX should be used with caution and being vigilant for the potential occurrence of severe infections particularly in fragile patients

- This is of interest in context of human antichimeric antibodies (HACAs). Such
- antibodies were detected at week 48 in 24.6% of rituximab-treated patients in the HERMES trial,although no association between the presence of HACAs and AEs or efficacy was seen


Fingolimod
Natalizumab
None
Rituximab
Ocrelizumab
Mild/Moderate
HSCT
Alemtuzumab
Cladribine
Mitoxantrone
Strong
INDUCTION EFFECT

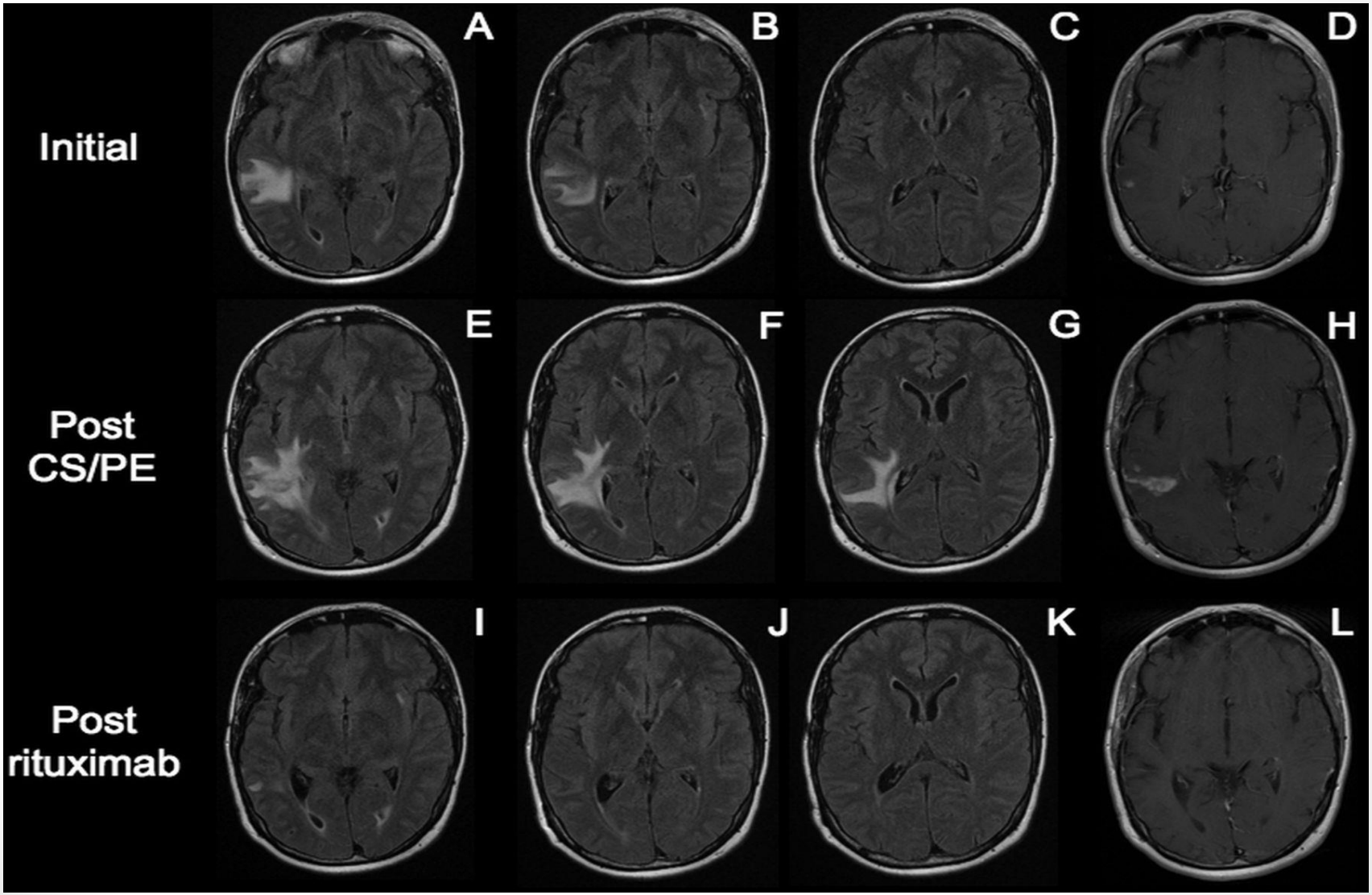
What is the best indication of RTX Injection IN multiple sclerosis patients?

Pt with Bcell pattern of MS

Tumefactive lesions

multiple GAD

Rituximab for tumefactive demyelination refractory to corticosteroids and plasma exchange



Patients with multiple cervical cord and normal brain lesions

Patients in the transition period and active MRI

Patients with good response to Plasma exchange

Preferred Treatment after TYSABRI and FINGO

In JCV seropositive patients

In the event of doubt, MS and NMO

If there is a simultaneous autoimmune disease

In the event of multiple optio spinal attacks

In the event of intolerance to treatment

TitlQuestion 1:
work up before starting rituximab

- CBC,
- HIV, hepatitis B, hepatitis C and VZV serology tests
- b-HCG (for women of childbearing age)
- chest X-ray

Question 2: vaccinations before starting rituximab and under treatment

- update the vaccination schedule, in particular vaccination against measles, and perform pneumococcal vaccination before starting RTX
- pneumococcal vaccination, start RTX after the first vaccine injection
- <65y perform VZV vaccination before starting RTX if the patient is not immunized against this virus
- between 65 and 74 y zoster vaccination before starting RTX, even if VZV serology is positive
- influenza vaccination every year under RTX
- perform recommended vaccinations under RTX without any preference concerning the optimal period for doing

Question 3:
timing of rituximab start

- Not recommend any therapeutic window between the end of the relapse treatment and the initiation of RTX

- If switch from a previous immunosuppressant to RTX, no delay after azathioprine or mycophenolate mofetil

- After cyclophosphamide or mitoxantrone infusion: neutrophil count has to be > 1500/mm3 to start RTX

Question 4:

modality of induction treatment
by rituximab

- 1 g two weeks apart" protocol for the treatment induction.
- mitigating RTX infusion-related events by:
- The use of IV methylprednisolone (100 mg) 1 hour prior to each RTX infusion , in combination with an anti-histaminic drug and paracetamol
- a slow titration of RTX infusion, especially at the first infusion

Question 5: infectious risk under rituximab and preventive measures

- Not recommend systematic pneumocystis prevention,but this prevention should be considered if T4 cells are below 200/mm3, as for HIV+ patients .
- Not recommend systematic zoster or herpes prevention by antiviral drug, but

  it should be considered in cases of zoster or recurrence of genital herpes under

  RTX
- Recommend a **systematic determination of immunoglobulinsubset (IgG, IgA, IgM, +/- IgG subclasses) amounts just before repeating RTX infusions** .
- **Supplementation by IV or immunoglobulins should be considered only in cases of recurrent infections coupled with low amounts of IgG (< 5 g/l)**
- Recommend a CBC at months 3 and 6 following the latest RTX infusion

Question 6: monitoring of RTX re-infusion: tools, rate and posology

- Recommend repeating RTX infusions every 6 months,except for patients who need a shorter retreatment interval because of an early CD27+ cell reemergence
- Recommend a CD27+ cell (and total CD19+ cells) count at any time in case of relapse, in order to distinguish **short responders** from patients for whom the RTX treatment has genuinely failed
- assess CD27+ cells at month 3 after the latest RTX infusion, and then once a month until month 6 after the latest RTX infusion, in the aim of detecting short responder patients .
- If it is not possible to perform this monthly analysis, we recommend a count

of CD27+ cells at least at months 3 and 6 after the latest RTX infusion

CD27+ cells are a subset of CD19+ cells (therefore also called CD19 + CD27+ cells)

corresponding to memory B-cells. Kim et al.have suggested that monitoring CD27+ cells in

Peripheral blood could optimize the maintenance regimen of RTX, by repeating treatment

only when CD27+ cells were above 0.05%. This strategy is supposedly more precise than the monitoring

Of CD19+ cells, since the risk of reactivation of the disease appears to be correlated with the

re-emergence of memory Bcells, but not with the re-emergence of the whole B-cell

population.

Question 7: therapeutic combination

Recommend using RTX only as a monotherapy in NMO-SD

except for steroids, which are used by some experts – mainly transiently while waiting

for the therapeutic coverage of RTX (given its onset of full

action estimated at 2 months) or, more rarely, in the long

term as an add-on therapy.

Question 8: pregnancy, breastfeeding

- NMO-SD women with childbearing potential should use effective contraceptive methods during treatment with RTX.
- Effective contraceptive methods during and for only 6 months following treatment with RTX, (EMA labelling advises such contraception for 12 months following treatment with RTX).
- Not consider that breastfeeding is contra-indicated if RTX was stopped before conception.


Thanks for
your attention.