Rituximab in rheumatic diseases

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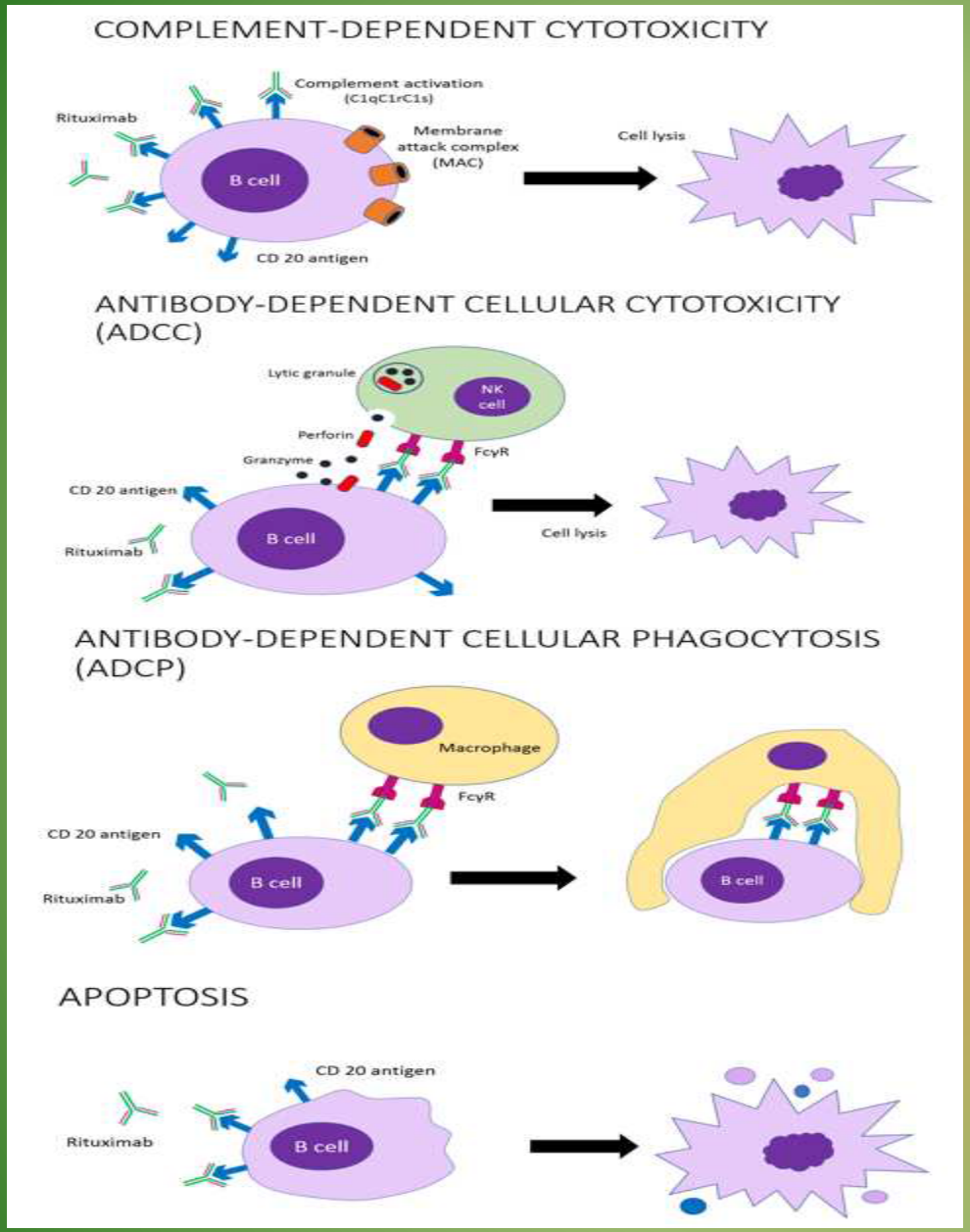
- Early diagnosis and treatment are essential for controlling ANCA-associated vasculitis disease progression and renal survival, but conventional therapies including **high doses of cyclophosphamide and glucocorticoids** cause acute and long-term side effects; thus, **rituximab is approved for remission induction and maintenance in ANCA-associated vasculitis**.
- Despite its widespread use and the risk of developing hypogammaglobinemia from rituximab, there have been different guidelines established for clinical **monitoring of hypogammaglobinemia**, which may preclude further use of rituximab in patients who would benefit from further course of rituximab.
- Among 113 rituximab-treated patients with ANCA-associated vasculitis (i.e., induction (n ¼ 30), maintenance (n ¼ 14), and combination (n ¼ 69)) at a large, single-tertiary referral center, we observed 26% (n ¼ 29) of the rituximab treated patients who developed a **decline in serum IgG to concentrations below 700 mg dL–1 and in 10% (n ¼ 11) who developed concentrations below 500 mg dL–1.**
- Our study demonstrates that of those who developed moderate or severe hypogammaglobinemia, the nadir IgM was observed after clinical visit 2 or 3, similar to the trend in the nadir of IgG post-rituximab therapy. **Comparison of the first Ig measurement after rituximab, repeat Ig measurements from follow-up were not statistically significant.**



Rituximab mechanisms for B-cell depletion

COMPLEMENT-DEPENDENT CYTOTOXICITY: Rituximab binds to the CD 20 antigen, and at the same time, complement binds to it activating the membrane attack complex on the B cell. This protein formation works as a channel tha allows water and ion influx that results in lethal colloid-osmotic swelling.

ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC): Fc[?]R receptors on Natural Killer (NK) cells can recognize the binding of rituximab to B cells and trigger degranulation and cell lysis.

ANTIBODY-DEPENDENT CELLULAR PHAGOCYTOSIS (ADCP): Once rituximab attaches to CD20 antigens, Fc[?]R receptors on macrophages or other phagocytic cells, can bind to the antibodies and trigger phagocytosis.

APOPTOSIS: Rituximab binding to CD 20 antigen can lead to direct signaling of apoptosis.

Randomized controlled trials in primary Sjögren syndrome.

Study	*N*	RTX dose and interval	Primary end point	Follow-up	SOC	Primary end point met?
Dass et al. [42]	17 (8 RTX vs. 9 placebo)	1 g IV W 0–2	Reduction of fatigue (> 20% on VAS)	6 months	Not further defined	Yes (RTX $p < 0{,}001$ vs. placebo $p = 0{,}147$)
Meijer et al. [43]	30 (20 RTX vs. 10 placebo)	1 g IV W 0–2	Improvement of stimulated salivary flow rate (ml/min)	48 weeks	Stop concomitant medication before baseline	Yes ($p = 0{,}038$)
TEARS [44]	120 (63 RTX vs. 57 placebo)	1 g IV W 0–2	Significant effect (≥ 30 mm) on ≥ 2 VAS (fatigue, sicca symptoms, global disease, pain)	24 weeks	Stop all immunosuppressive medication 4 weeks before baseline	No
TRACTISS [45]	133 (67 RTX vs. 66 placebo)	1 g IV W 0–2 W 24–26	Significant effect on fatigue, oral dryness (VAS)	48 weeks	Stable dose GC and hydroxychloroquine	No

RCT, randomized controlled trial; N, number of patients included; SOC, standard of care; IV, intravenously; W, week; VAS, visual analog scale; RTX, rituximab; ml, milliliter; GC, glucocorticoids.

. Indications for rituximab in systemic autoimmune rheumatic disease.

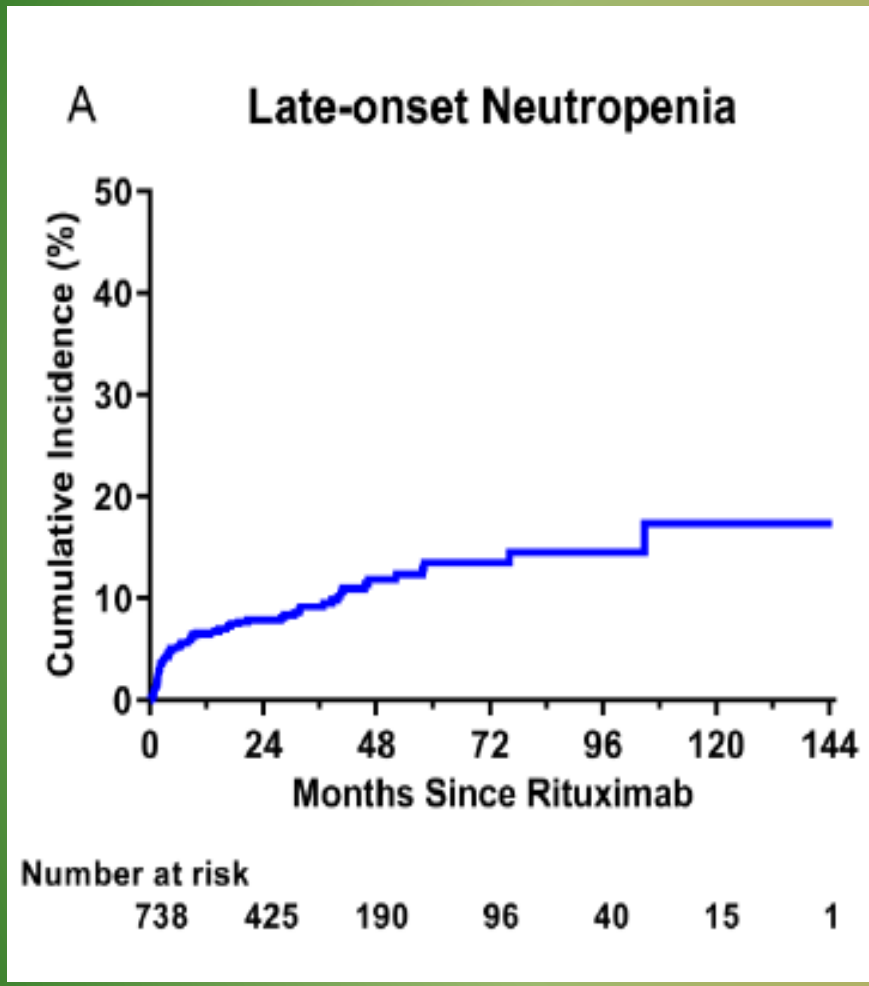
SARD	Indication	Combination therapy?	Single course or to be repeated?	Guidelines endorsement (LOE, SOR)
SLE	Refractory moderate-to-severe SLE	On top of SOC	To be repeated	BSR (2+, C) [12] ACR (C)
SSc	Refractory skin involvement	On top of SOC	To be repeated	BSR (III, C) [38]
	SSc-associated ILD	On top of SOC	To be repeated	No formal recommendation
pSS	Systemic involvement	On top of SOC	To be repeated	ACR (Moderate) [52] BSR (IIb, B) [40]
IIM	Refractory myositis	On top of GC	Single course	No guidelines available

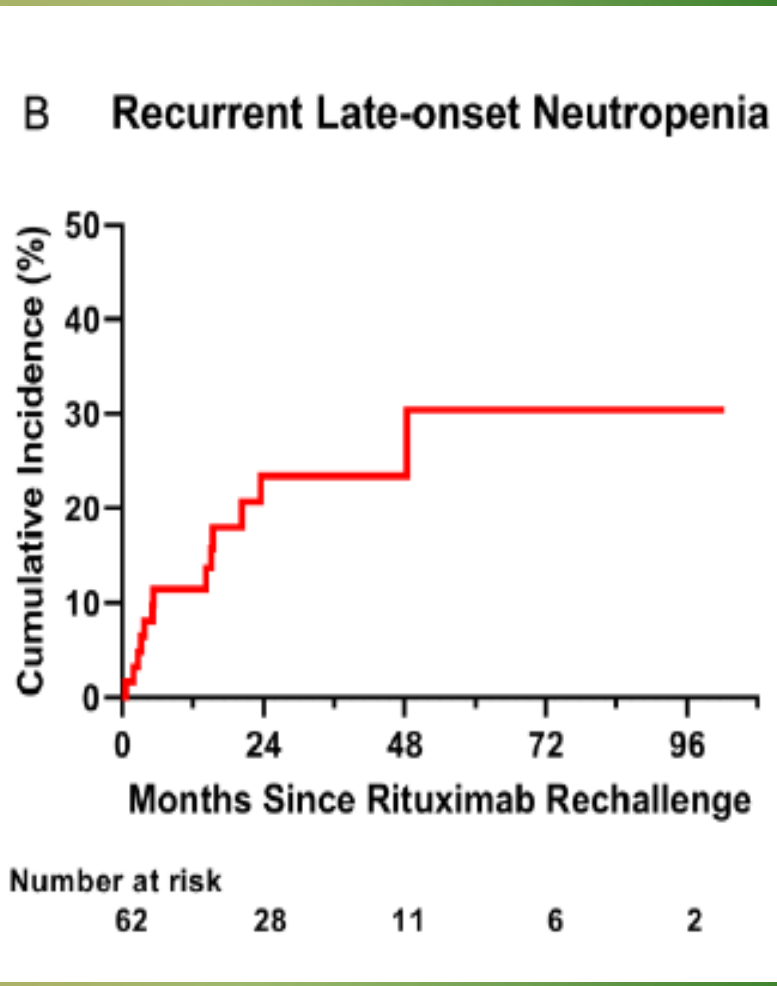
SARD, systemic autoimmune rheumatic disease; LOE, level of evidence; SOR, strength of recommendation; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; pSS, primary Sjögren syndrome; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; SOC, standard of care; GC, glucocorticoids; BSR, British Society of Rheumatology; ACR, American College of Rheumatology.

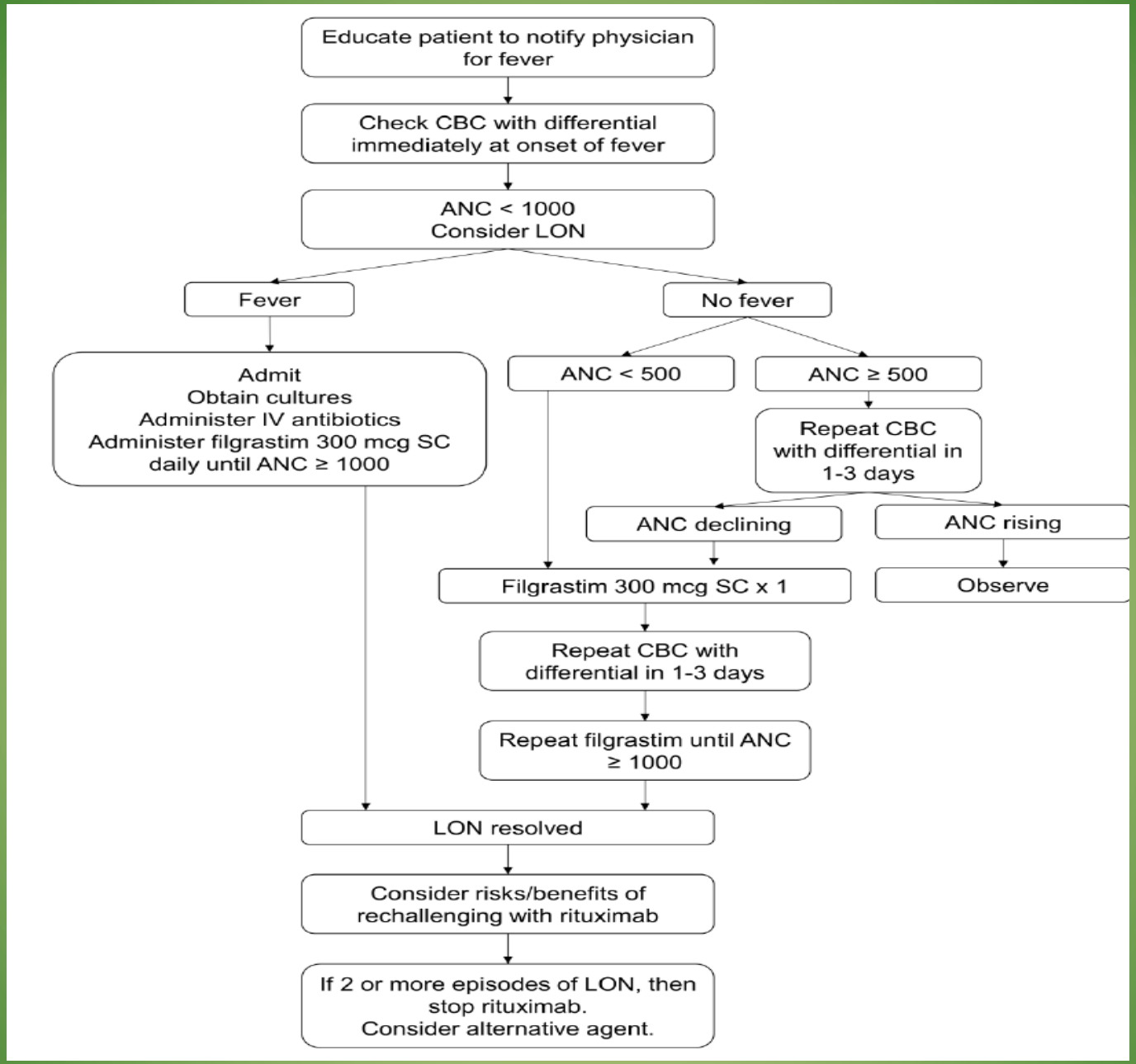
Upcoming phase-2 and -3 trials of rituximab in systemic autoimmune rheumatic disease.

Trial	Phase	Indication	Intervention + comparison if applicable	Primary outcome measure (time)	Status
RECITAL [63]	2/3	CTD-ILD	RTX vs. CYC	Absolute change in FVC (W 48)	Recruiting
BLISS-BELIEVE [72]	3	SLE	BEL + RTX + SOC vs. BEL + placebo + SOC vs. BEL + SOC	Disease control (W 52)	Not yet recruiting
ROOTS [73]	2	SLE: skin disease, arthritis	RTX + CS vs. CS	Feasibility of trial (W 24)	Recruiting
RITUXILUP [74]	3	Lupus nephritis	RTX + CS + MMF vs. CS + MMF	Complete renal response without need of PO CS (W 52)	Terminated
SYNBloSe [75]	2	Lupus nephritis	BEL + RTX	Reduction of pathogenic autoantibodies (W 24)	Enrolling
RECOVER [76]	2/3	SSc: articular symptoms	RTX vs. placebo	Number of tender and swollen joints out of 53 joints (W 26)	Completed
NC02631538 [77]	2	pSS	BEL + RTX vs. BEL vs. RTX vs. placebo	Number of SAEs and AESIs (W 104)	Recruiting
EvER-ILD [78]	3	ILD, NSIP pattern	RTX + MMF vs. MMF	Change in FVC (W 24)	Recruiting

CTD, connective tissue disease; ILD, interstitial lung disease; RTX, rituximab; CYC, cyclophosphamide; FVC, forced vital capacity; W, week; SLE, systemic lupus erythematosus; BEL, belimumab; CS, corticosteroids; PO, peroral; MMF, myophenolate mofetil; SSc, systemic sclerosis; SAE, severe adverse event; AESI, adverse events of special interest; NSIP, non-specific interstitial pneumonia; vs., versus.


A
Late-onset Neutropenia
Cumulative Incidence (%)
50
40
30
20
10
0
0
24
48
72
96
120
144
Months Since Rituximab
Number at risk
738
425
190
96
40
15
1


B
Recurrent Late-onset Neutropenia
Cumulative Incidence (%)
50
40
30
20
10
0
0
24
48
72
96
Months Since Rituximab Rechallenge
Number at risk
62
28
11
6
2


Educate patient to notify physician for fever
Check CBC with differential immediately at onset of fever
ANC < 1000
Consider LON
Fever
No fever
Admit
Obtain cultures
Administer IV antibiotics
Administer filgrastim 300 mcg SC daily until ANC ≥ 1000
ANC < 500
ANC ≥ 500
Repeat CBC with differential in 1-3 days
ANC declining
ANC rising
Filgrastim 300 mcg SC x 1
Observe
Repeat CBC with differential in 1-3 days
Repeat filgrastim until ANC ≥ 1000
LON resolved
Consider risks/benefits of rechallenging with rituximab
If 2 or more episodes of LON, then stop rituximab.
Consider alternative agent.

Baseline predictors of serious infection in the 12 months following RTX initiation (cycle 1)*

Characteristic	No serious infection (n = 625)	Serious infection (n = 75)	Univariable analysis OR (95% CI)	Univariable analysis P (with multiple imputation)	Multivariable analysis OR (95% CI)	Multivariable analysis P (with multiple imputation)
Age, median (IQR) years†	57.1 (45.4, 66.4)	64.5 (53.7, 72.8)	1.27 (1.07–1.50)	0.005	–	–
Female sex, no. (%)	497 (79.5)	53 (70.6)	0.62 (0.36–1.06)	0.080	–	–
Disease duration, median (IQR) years‡	7.9 (3.5, 14.9)	8.4 (2.9, 16.4)	1.0 (0.98–1.03)	0.517	1.03 (0.99–1.06)	0.100
Ever smoked, no. (%)	259 (41.4)	40 (53.4)	1.70 (1.00–2.61)	0.051	–	
Previous history of any cancer, no. (%)	46 (7.4)	11 (14.7)	2.16 (1.07–4.39)	0.032	3.22 (1.32–7.83)	0.010
Chronic lung disease, no. (%)	129 (20.6)	31 (41.3)	2.71 (1.65–4.46)	<0.001	1.79 (0.96–3.34)	0.069
Heart failure, no. (%)	11 (1.8)	2 (2.7)	1.53 (0.33–7.03)	0.585	-	
Diabetes mellitus, no. (%)	33 (5.3)	9 (12.0)	2.45 (1.12–5.33)	0.025	1.88 (0.71–4.94)	0.201
Diagnosis of RA vs. CTDs, no. (%)	457 (73.1)	50 (66.7)	0.74 (0.44–1.24)	0.249	0.49 (0.22–1.07)	0.073
Previous severe infection, no. (%)	58 (9.3)	40 (53.3)	11.17 (6.59–18.94)	<0.001	9.29 (4.93–17.51)	<0.001

Previous cyclophosphamide, no. (%)	123 (19.7)	19 (25.3)	1.38 (0.79–2.42)	0.252	–	
Previous biologics, no. (%)§			0.82 (0.64–1.04)	0.102	0.84 (0.68–1.04)	0.113
0	316 (50.5)	48 (64.0)	–	–	–	–
1	137 (21.9)	11 (14.7)	–	–	–	–
2	105 (16.8)	10 (13.3)	–	–	–	–
3	52 (8.3)	4 (5.3)	–	–	–	–
4	15 (2.4)	2 (2.7)	–	–	–	–
Concomitant corticosteroid, no. (%)	256 (41.0)	47 (62.7)	2.41 (1.48–3.97)	<0.001	–	–
Corticosteroid dose, median (IQR) mg/day	0 (0, 7.5)	5 (0, 10)	1.04 (1.01–1.07)	0.007	1.03 (0.99–1.07)	0.151
Concomitant csDMARDs, no. (%)	470 (75.2)	44 (58.7)	0.47 (0.29–0.77)	0.003	0.63 (0.35–1.14)	0.128
RTX-associated neutropenia, no. (%)	6 (0.96)	5 (6.67)	7.37 (2.19–24.77)	0.001	13.26 (3.12–56.44)	<0.001
Low IgM (<0.5 gm/liter), no. (%)	42 (6.7)	15 (20.0)	3.47 (1.82–6.63)	<0.001	2.07 (0.86–4.99)	0.103
Low IgA (<0.8 gm/liter), no. (%)	11 (1.8)	4 (5.3)	3.14 (0.98–10.14)	0.055	–	
Low IgG (<6.0 gm/liter), no. (%)	20 (3.2)	14 (18.7)	7.28 (3.48–15.25)	<0.001	2.80 (1.02–7.67)	0.045
Naive B cells, median (IQR)¶	72.2 (29.7, 122.0)	43.3 (9.5, 102.0)	1.000 (0.997–1.002)	0.728	–	–
Memory B cells, median (IQR)¶	18.5 (8.3, 35.5)	10.7 (5.0, 39.1)	0.999 (0.992–1.006)	0.743	–	–
Plasmablasts, median (IQR)¶	1.9 (0.8, 3.8)	1.9 (0.9)	1.016 (0.991–1.043)	0.215	1.02 (0.991–1.051)	0.173

* RTX = rituximab; 95% CI = 95% confidence interval; IQR = interquartile range; RA = rheumatoid arthritis; CTDs = connective tissue diseases; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs.
† Odds ratio (OR) is per 10 years of age.
‡ ORs are per year.
§ ORs are per number of previous biologics.
¶ B cell count is $\times 10^9$ cells/liter; for each subset multiply by 1,000 prior to analysis.

Predictors of serious infection during RTX cycles 2–4*

Characteristic	No serious infection (n = 1,208)	Serious infection (n = 111)	Univariable analysis OR (95% CI)	Univariable analysis P	Multivariable analysis OR (95% CI)	Multivariable analysis P
Age, mean ± SD years†	55.5 ± 14.8	59.8 ± 15.7	1.03 (1.00–1.05)	0.007	–	–
Female sex, %	80.1	73.0	0.64 (0.35–1.17)	0.149	0.70 (0.39–1.24)	0.219
Previous history of any cancer, %	9.0	14.4	1.93 (0.86–4.35)	0.112	3.24 (1.50–7.01)	0.003
Chronic lung disease, %	19.6	39.6	3.51 (1.94–6.35)	<0.001	2.24 (1.25–4.02)	0.007
Heart failure, %	1.2	5.4	2.60 (0.87–7.80)	0.087	5.75 (1.45–22.80)	0.013
Diabetes mellitus, %	5.9	13.5	9.42 (1.87–47.53)	0.007	2.61 (1.14–5.97)	0.023
Previous severe infection, %	8.9	37.8	10.10 (4.94–20.65)	<0.001	6.32 (3.11–12.82)	<0.001
Corticosteroid dose, median (IQR) mg/day	0 (0, 5)	3.75 (0, 7.50)	1.11 (1.05–1.16)	<0.001	1.08 (1.02–1.13)	0.005
Concomitant csDMARDs, %	64.0	59.5	0.80 (0.47–1.35)	0.395	–	–
Full-dose RTX, %	93.3	91.9	0.65 (0.26–1.62)	0.351	–	–
Time to RTX re-treatment, median (IQR) weeks	49.3 (36.4, 64.7)	53.0 (38.4, 86.7)	1.01 (1.00–1.01)	0.003	1.01 (1.00–1.02)	0.003
RTX-associated neutropenia, %	0.58	3.60	8.07 (1.53–42.72)	0.014	16.56 (3.82–71.72)	<0.001
IgM, mean ± SD gm/liter	0.95 ± 0.78	0.97 ± 1.57	1.05 (0.82–1.33)	0.719	1.24 (0.96–1.60)	0.094
IgA, mean ± SD gm/liter	2.84 ± 1.44	2.74 ± 1.61	0.93 (0.77–1.11)	0.399	–	–
IgG, mean ± SD gm/liter	11.06 ± 3.79	9.81 ± 4.30	0.89 (0.83–0.96)	0.002	0.88 (0.81–0.96)	0.005
Percentage change in IgM level, median (IQR)	36.2 (22.5, 50.0)	36.3 (19.2, 58.2)	1.00 (0.99–1.01)	0.800	–	–
Percentage change in IgA level, median (IQR)	8.7 (−3.3, 20.4)	9.0 (−5.9, 28.4)	1.01 (1.00–1.02)	0.190	–	–
Percentage change in IgG level, median (IQR)	10.2 (−0.80, 20.6)	13.8 (0.0, 28.1)	1.01 (0.99–1.02)	0.381	–	–
Pre-RTX naive B cells, median (IQR)‡	16.2 (1.7, 51.5)	5.8 (0.2, 35.2)	1.001 (0.998–1.003)	0.565	1.002 (0.993–1.005)	0.139
Pre-RTX memory B cells, median (IQR)‡	1.4 (0.6, 3.3)	1.3 (0.4, 4.0)	0.993 (0.958–1.030)	0.719	0.970 (0.928–1.014)	0.176
Pre-RTX plasmablasts, median (IQR)‡	1.0 (0.3, 2.1)	0.8 (0.0, 2.7)	1.005 (0.950–1.062)	0.867	–	–
Complete B cell depletion, %	73.4	72.1	0.80 (0.46–1.40)	0.435	0.65 (0.39–1.24)	0.191

* RTX = rituximab; 95% CI = 95% confidence interval; IQR = interquartile range; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs.
† Odds ratio (OR) is per 10 years of age.
‡ B cell count is $\times 10^9$ cells/liter; for each subset multiply by 1,000 prior to analysis.

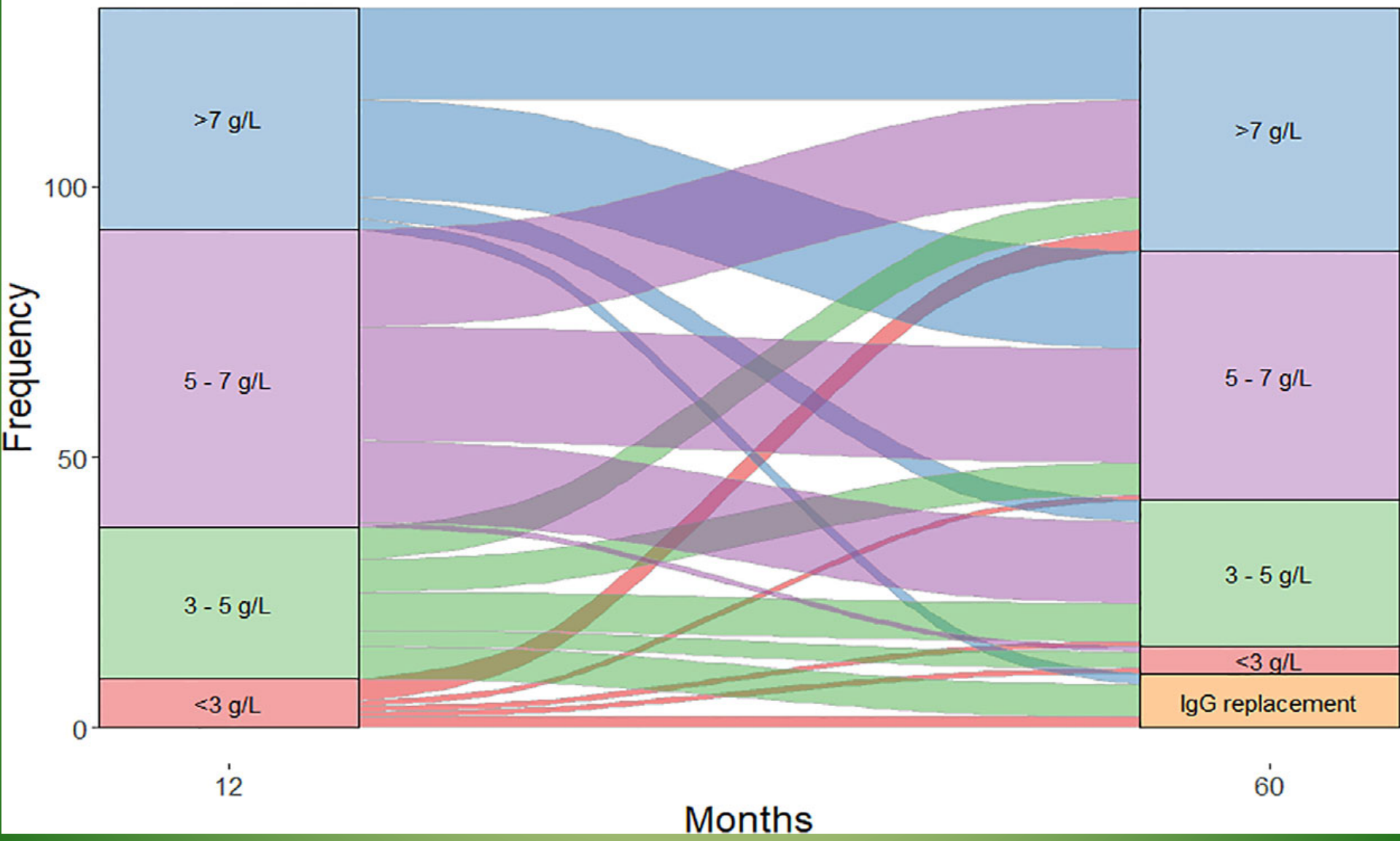
Serious infection rates in patients with IgM and IgG levels less than the LLN for at least 4 months during RTX therapy*

	Group 1, Ig < LLN at RTX initiation (n = 57)	Group 2, developed Ig < LLN during RTX (n = 161)		Group 3, did not develop Ig < LLN during RTX (n = 482)
		Before Ig < LLN	During/after Ig < LLN	
IgM				
Total exposure, no. person-years	235.5	538.1	528.2	1,700.9
SIEs, no.	25	53	74	156
Rate of SIE per 100 person-years (95% CI)	10.6 (6.9–15.7)	9.8 (7.4–12.9)	14.0 (11.0–16.6)	9.2 (7.8–10.7)
IgG				
Total exposure, no. person-years	122.1	123.5	136.0	2,457.1
SIEs, no.	20	15	29	238
Rate of SIE per 100 person-years (95% CI)	16.4 (10.0–25.3)	12.1 (6.8–20.0)	21.3 (14.3–30.6)	9.7 (8.5–11.0)

* LLN = lower limit of normal; RTX = rituximab; SIEs = serious infection events; 95% CI = 95% confidence interval.

Immunoglobulin levels should be monitored at **baseline and before each RTX cycle**, particularly in patients with **comorbidities and low baseline immunoglobulin levels**, in order to discern those at risk of SIEs. Individualized risk–benefit assessment regarding **RTX re-treatment decisions** is needed in those **with lower IgG** since this is a **consistent predictor of SIE and may increase infection profiles** when RTX is switched to different bDMARDs.

IgG after Rituximab



RTX. associated with hypogammaglobulinemia:

- The use of prior immunosuppressive therapies
- prolonged glucocorticoid use and
- female gender
- multi-system autoimmune disease

Hypogammaglobulinemia at visit 1, n (%)	N = 47
Mild: IgG level 450-700 mg dL^{-1}	33 [70.2]
Moderate: IgG level 200-450 mg dL^{-1}	13 [27.7]
Severe: IgG level $\leq$200 mg dL^{-1}	1 [2.1]

- **Rituximab** is indicated for patients with
- **severe active RA who have an inadequate response or intolerance to one or more TNFis**
- however, it is also used **as first bDMARD in patients with contraindication to these drugs.**
- **ILD due to RA**

- Several possible **rituximab/DMARD combinations** have been assessed (including **MTX & leflunomide**), showing apparent efficacy.
- Response to treatment seems to be determined by the **degree of B-cell depletion** and not by the dose of rituximab.

- Quartuccio et al. stated that it was **RF positivity and not ACPA positivity** that is associated **with better EULAR responses**.
- Results show that a **high IFN signature** is associated with **poor response to rituximab**.
- Several articles have confirmed a **decrease in CD4+ T-cells** following **rituximab** administration in RA patients showing clinical response.
- Whereas short term studies have reported **maintained levels of IgM and IgG** , long-term trials observed a decrease, **particularly of IgM after rituximab treatment**. Registry data shows that lower **IgG levels before rituximab administration (<6 g/l)** are associated with higher risk of serious infection events.

- Some risk factors related to **hypogammaglobulinemia** are **older age, chronic lung disease, and previous history of cancer**. In all patients, but especially in these cases, **immunoglobulin quantification should be done before and after each rituximab administration**.
- Some malignancies have been described after exposure to rituximab. The most commonly reported ones are **skin neoplasms, and breast cancer.**