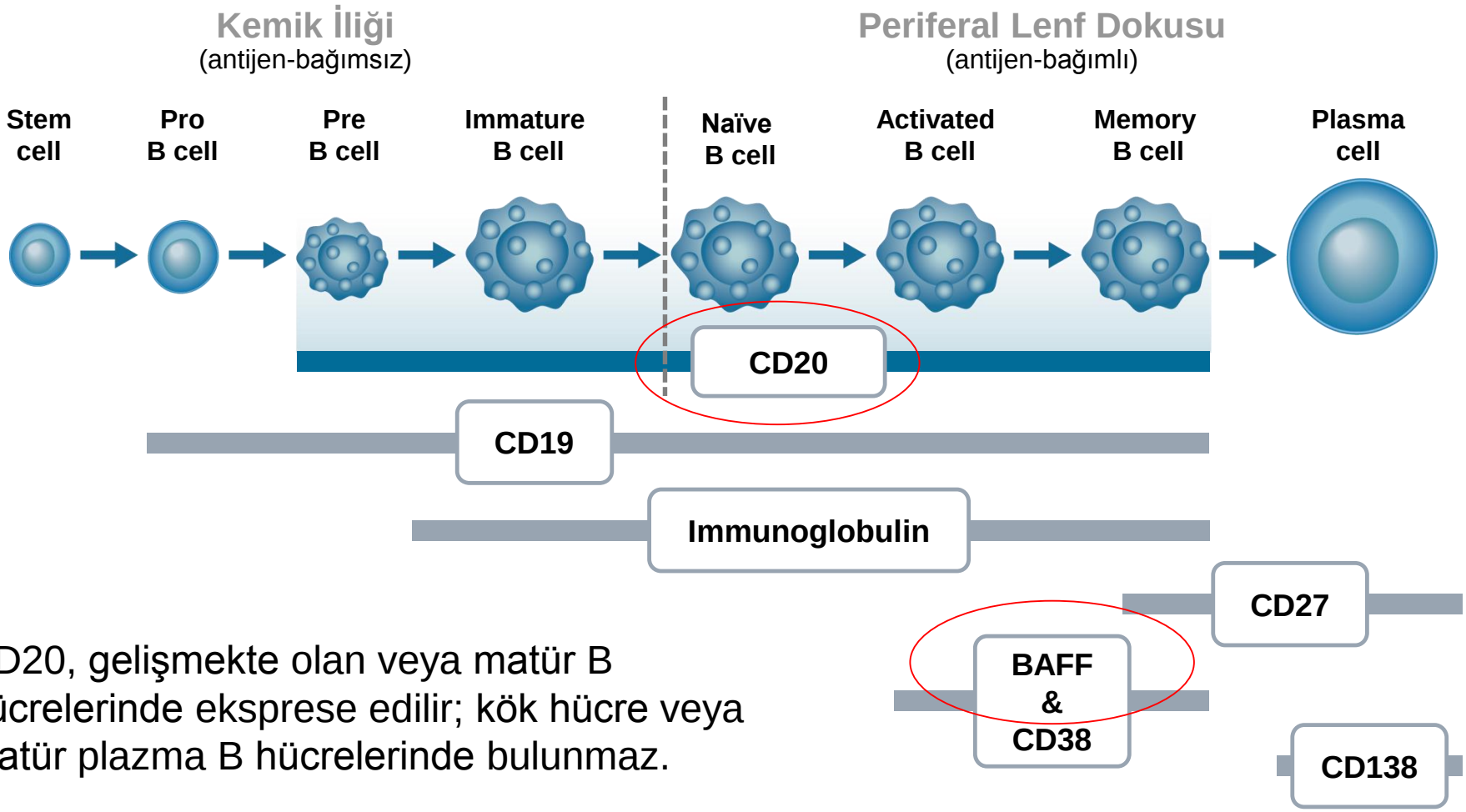
Yeni Çalışmalar Akılcı İlaç Kullanımı Konusunda Hangi İpuçlarını Veriyor

B Hücresine Yönelik Tedaviler

Prof. Dr. Sedat Kiraz

B Hücrelerine Özgü Hedefler



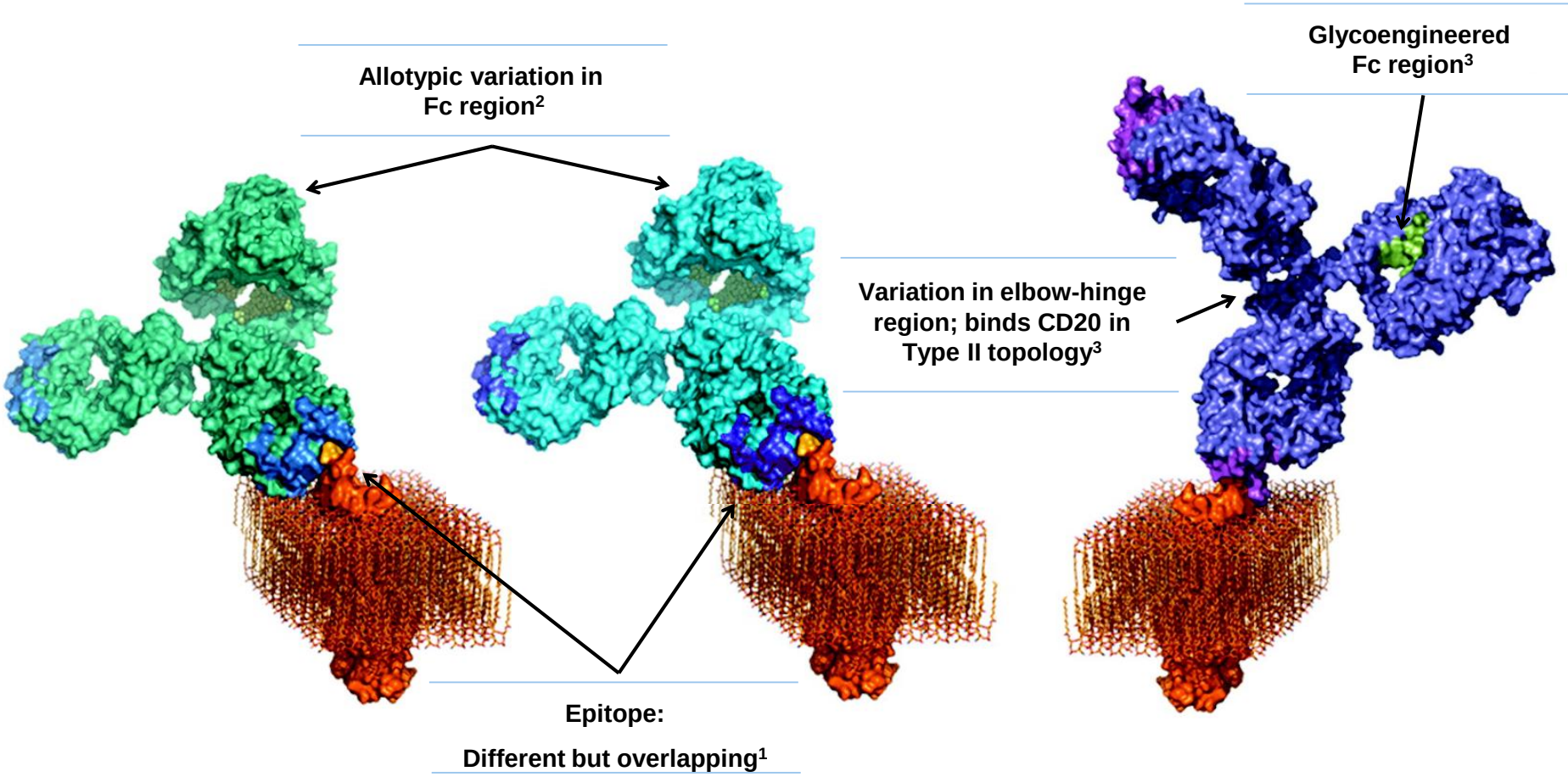
CD20, gelişmekte olan veya matür B hücrelerinde eksprese edilir; kök hücre veya matür plazma B hücrelerinde bulunmaz.

BAFF, B-cell activating factor belonging to the TNF family; CD, cluster of differentiation.
Society of Transplantation and the American Society of Transplant Surgeons. Winiarska M, et al. *Front Biosci* 2011;16:277–306.

B Hücre Deplesyonuna Yönelik Ruhsatlı Anti-CD20 Tedaviler

Rituksimab (RTX)	▪ Hodgkin-dışı Lenfoma ▪ Kronik Lenfositik Lösemi (KLL) ▪ Romatoid Artrit (RA) ▪ Granülamatöz Polianjiitis (Wegener) (GPA) ve Mikroskobik Polianjiitis (MPA) ▪ SLE
Okrelizumab (OCR)	▪ Multipl Skleroz (RMS ve PPMS)
Obinutuzumab (OBI)	▪ Kronik Lenfositik Lösemi

RTX, OCR ve OBI Arasında Yapısal Farklılıklar



Rituksimab
Kimerik IgG_1

Tip I

Okrelizumab
Humanize IgG_1

Tip I

Obinutuzumab
Humanize IgG_1

Tip II

1. Polyak MJ, Deans JP. *Blood* 2002;99:3256–3262; 2. Morschhauser F, et al. *Ann Oncol* 2010;21:1870–1876; 3. Klein C et al. *mAbs* 2013;5:22–33.

Anti CD20 Mab'lar Sınıflama

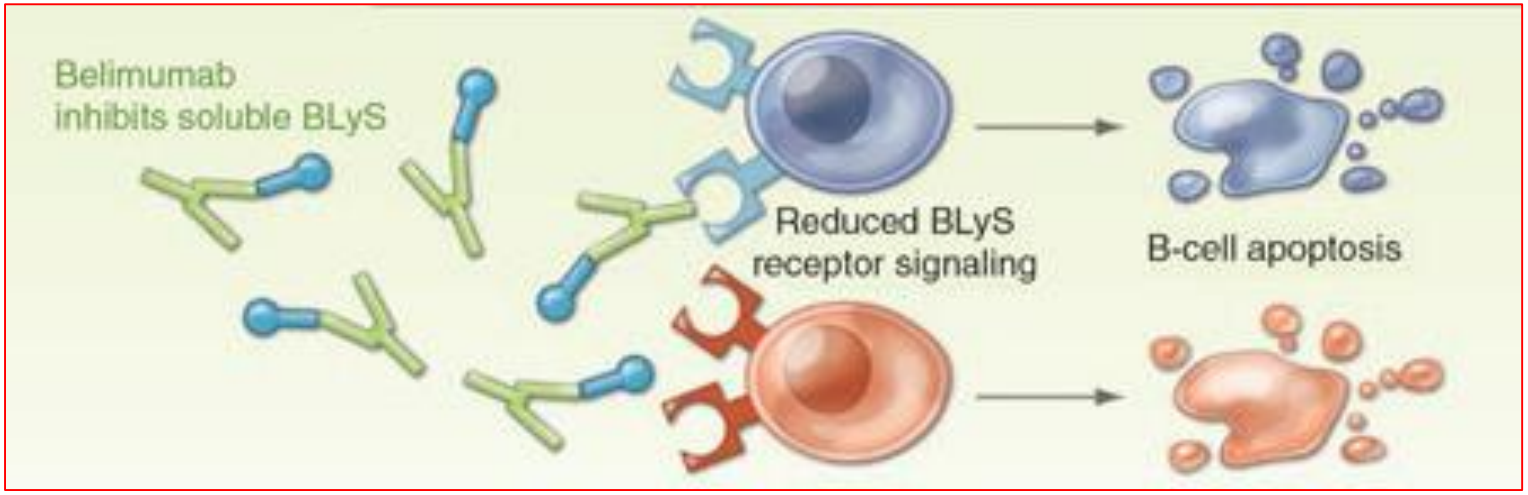
Characteristics of type I and II anti-CD20 monoclonal antibodies.

	Type I	Type II
Established mAb	Rituximab [1] Ofatumumab [2] Ocrelizumab [3] AME133v46 [4] PRO131921 [5] TRU015[a] [6,7] Veltuzumab [8]	Obinutuzumab [9] Tositumomab [10] 11B8 [11]
In clinical or trial use in RA and/or SLE	Rituximab Ofatumumab Ocrelizumab	Obinutuzumab
Redistributes CD20	Yes	No
Internalization of anti-CD20 mAb complexes	Yes, but highly variable	To a small extent and significantly less than rituximab
Homotypic aggregation	Weak	Strong
CD20 tetramer to mAb binding ratio	1:1	2:1
CDC	Potent	Weak
ADCC	Yes	Yes
ADCP	Yes	Yes
DCD	Apoptosis	Nonapoptotic lysosome-mediated cell death

[a] TRU-015 is a single-chain Fv generated from 2H7 linked to human IgG1 but devoid of CH1 and CL domains. The original mAb was type I [12].*Abbreviations*: RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; CDC, complement-dependent cellular cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cell phagocytosis; DCD, direct cell death.

Anti-CD20 Dışındaki B Hücrelere Yönelik Tedaviler: BELİMUMAB

- TNF ailesinin bir üyesi olan B Lenfosit Stimülatörü (BLyS, BAFF ve TNFSF13 olarak da adlandırılır), B hücre apoptozunu baskılar ve B hücrelerinin immünglobulin üreten plazma hücresine farklılaşmasını uyarır.
- Belimumab, humanize IgG1 monoklonal antikorudur ve çözünebilir insan B Lenfosit Stimülatörüne bağlanarak biyolojik aktivitesini baskılar.
- Otoantikoru pozitif SLE hastalarında endikedir.



RİTUKSİMAB

Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial

Duncan Porter, Jurgen van Melckebeke, James Dale, C Martina Messow, Alexander McConnachie, Andrew Walker, Robin Munro, John McLaren, Euan McRorie, Jon Packham, Christopher D Buckley, John Harvie, Peter Taylor, Ernest Choy, Costantino Pitzalis, Iain B McInnes

Lancet 2016; 388: 239–47

- Anti TNF vs RTX etkinlik, güvenlilik ve maliyet karşılaştırması
- Açık, ramdomize kontrollü
- RF/CCP+, DMARD dirençli, 35 merkez
- 1:1 randomizasyon
- Grup1: 1g RTX 1-15. gün (yanıt varsa 26 hf sonra)
- Grup2: Anti TNF ADA, ETA
- Primer sonlanım DAS 28 (ESR) 12. ayda (6. ayda ara değerlendirme)
- N:295 (RTX:144, AntiTNF: 151)
- DAS28ESR RTX -2.6 vs AntiTNF -2.4 (Non inferiory sınırında p:0.24)
- RTX 9405 vs Anti TNF 11523 Pound ($p<0.001$)
- Yan etkiler benzer

Cost-effectiveness of rituximab strategies in rheumatoid arthritis

SciencePhoto

We read with interest the Article by Duncan Porter and colleagues (July 16, p 239),[1] and the accompanying comment by Tom Huizinga and colleagues (July 16, p 213).[2] The results of this head-to-head trial[1] showed that a treatment strategy with rituximab as a first-line biological drug was not inferior to a strategy with inhibitors of tumour necrosis factor (TNF), and also suggested that this strategy was associated with substantially lower health-related costs. Even if this economic assessment could be debated, because it has been made in the context of the UK health system and is not necessarily transposable to other health systems, the study is very

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Huizinga and colleagues suggest in their comment that the side-effect profile of rituximab is different from a TNF inhibitor, especially because of the theoretical risk of progressive multifocal leukoencephalopathy. However, it is a very rare complication that almost exclusively occurs in patients who have received highly immunosuppressive drugs, and can also occur with other biological drugs.[10] By contrast, the risk of tuberculosis associated with anti-TNF is not negligible, even after antibiotic prophylaxis, and this risk of tuberculosis does not seem to be increased with rituximab. Therefore, low-dose rituximab, either from the start of treatment or after a first course at full dose, could be considered in patients with rheumatoid arthritis as a first-line option of biological treatment, especially in developing countries where health cost is a considerable issue and where the risk of tuberculosis remains. The arrival of rituximab biosimilars will decrease the cost of this low-dose rituximab strategy, and help to make biological treatment available worldwide for all patients with rheumatoid arthritis who need it.

Reumatol Clin. 2016;12(6):319–322

Sociedad Española de Reumatología - Colegio Mexicano de Reumatología

Reumatología Clínica

www.reumatologiaclinica.org

Brief Report

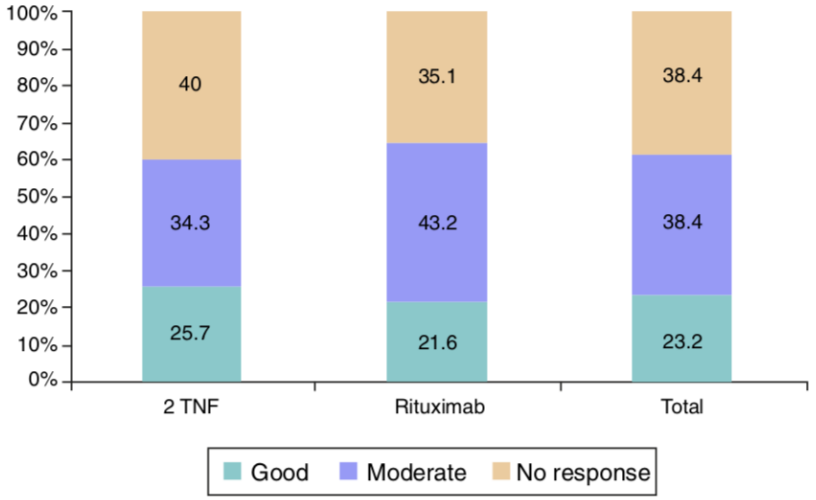
VARIAR Study: Assessment of Short-term Efficacy and Safety of Rituximab Compared to an Tumor Necrosis Factor Alpha Antagonists as Second-line Drug Therapy in Patients With Rheumatoid Arthritis Refractory to a First Tumor Necrosis Factor Alpha Antagonist☆

Vicenç Torrente-Segarra,[a,*] Asunción Acosta Pereira,[b] Rosa Morla,[c] José Miguel Ruiz,[d]

Baseline Sociodemographic and Clinical Variables.

	Rituximab (*n*=54)	*2 TNF* (*n*=49)	*Total* (*n*=103)
Age (years)	58.0 ± 14.1	50.9 ± 12.3	57.4 ± 13.0
Gender (female, %)	77.7%	67.3%	73.7%
Duration of RA (years)	5.7 ± 3.2	6.1 ± 2.9	5.8 ± 3.6
DAS28	5.45 ± 1.5[a]	5.18 ± 1.8[a]	5.37 ± 1.7
HAQ	1.2 ± 0.8	1.0 ± 0.7	1.1 ± 0.7
TJC	8.6 ± 4.5	6.6 ± 4.1	
SJC	8.8 ± 4.1	7.5 ± 3.7	
ESR (mmHg)	41.0 ± 24.1	38.7 ± 22.9	40.5 ± 26.4
CRP (mg/dL)	27.6 ± 18.4	21.4 ± 12.7	24.7 ± 15.0
Rheumatoid factor			
Titer (U/mL)	99.6 ± 80.2	82.7 ± 64.7	91.2 ± 73.4
% (positive)	70.2%	75.7%	72.8%
ACPA (positive)	50.2%	53.1%	51.4%
Previous TNF			
Etanercept	31%	32%	33%
Infliximab	25%	22%	26%
Adalimumab	44%	46%	41%
Reason for discontinuing previous TNF			
-Primary inefficacy	93%	94%	93%
Secondary inefficacy	5%	0%	4%
Adverse effect and/or intolerance	2%	6%	3%
Concomitant use of methotrexate	92.5%	77.5%	87.3%

Prospektif gözlemsel çok merkezli
Bir anti-TNF dirençli RA hastaları
RTX veya 2.anti-TNF (2TNF) alıyor
,



No significant differences (P > .05) between the 2 groups

Fig. 1. EULAR response rate after 6 months. No significant differences (*P*>.05) between the 2 groups. EULAR, European League Against Rheumatism.

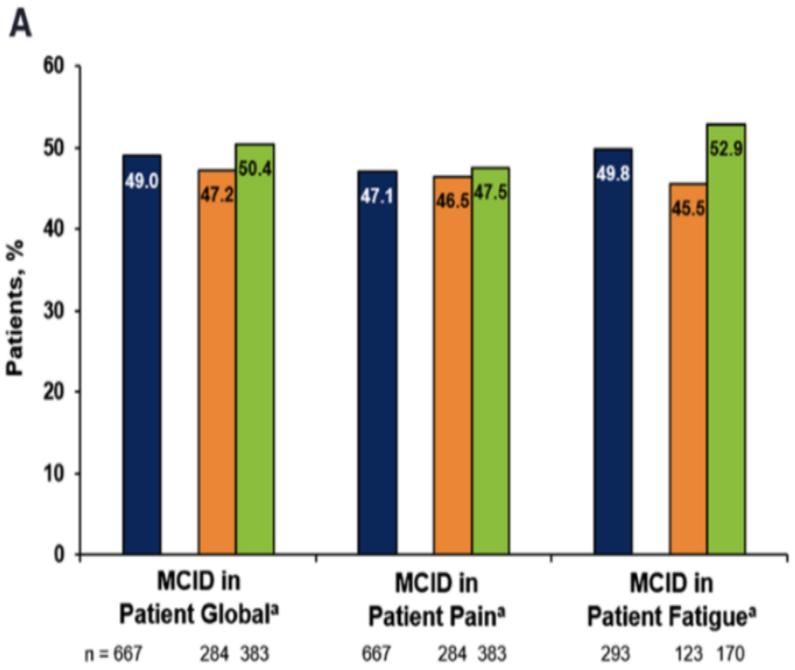
Clin Rheumatol (2017) 36:2135–2140
DOI 10.1007/s10067-017-3742-2

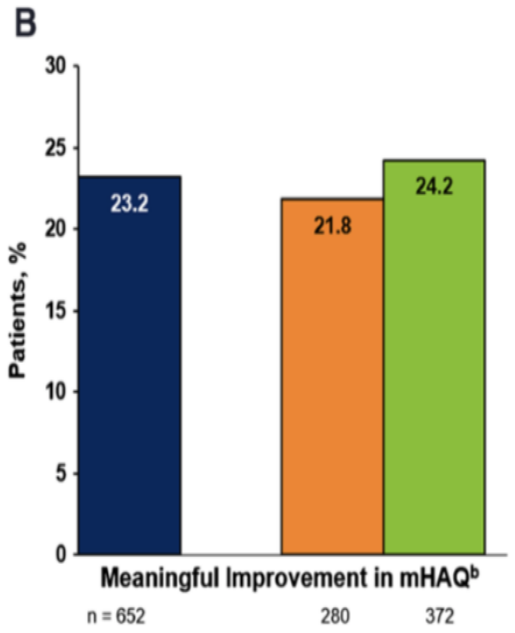
BRIEF REPORT

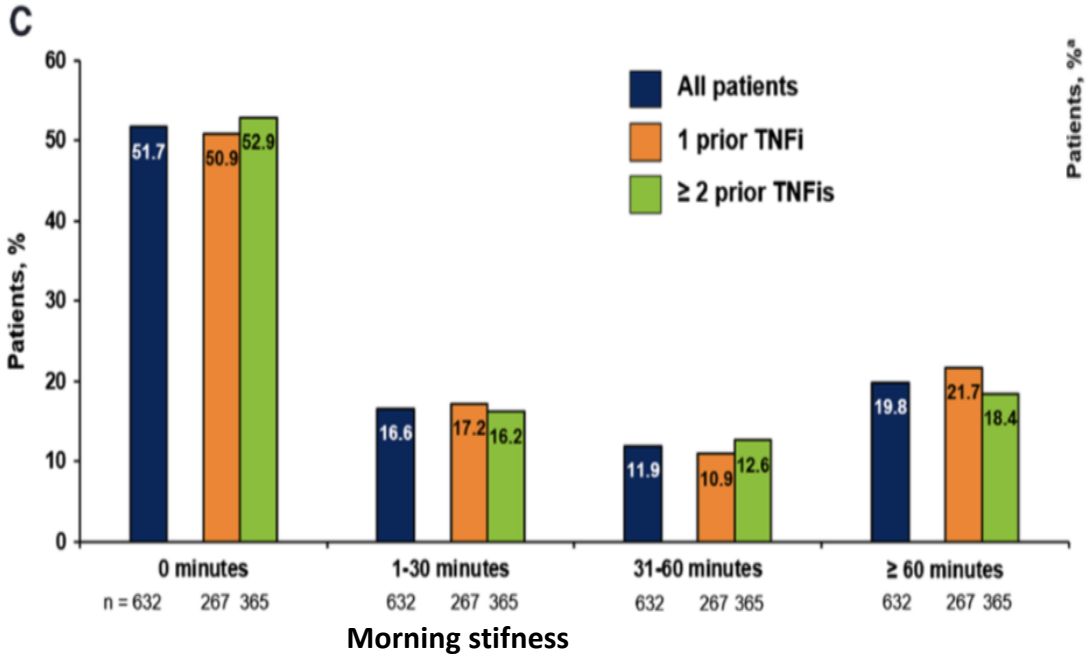
Impact of rituximab on patient-reported outcomes in patients with rheumatoid arthritis from the US Corrona Registry

Leslie R. Harrold[1,2] · Ani John[3] · Jennie Best[3] · Steve Zlotnick[3] · Chitra Karki[2] ·

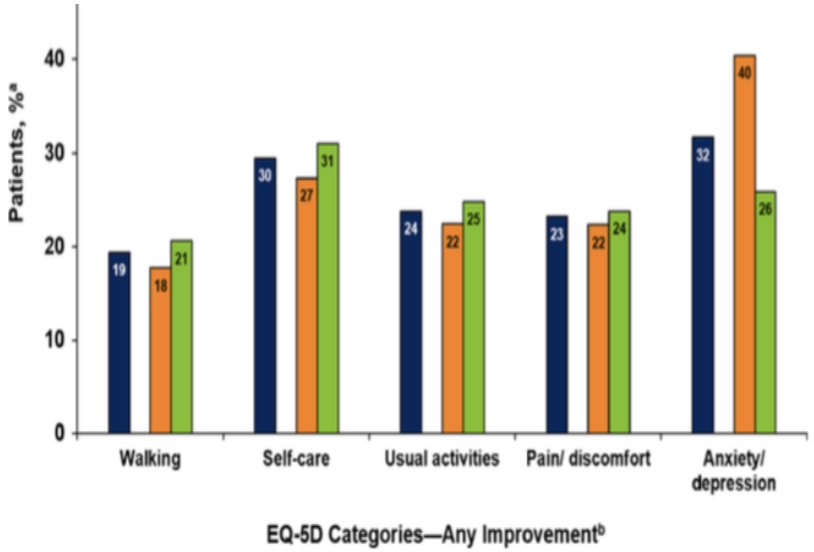
- **667 aktif RA (≥1 anti-TNF kullanımı ve yeni RTX başlanan)**
  - ✓%54 hastada yüksek hastalık aktivitesi PRO (hasta temelli sonlanımlar) RTX başlanmasından 1 yıl sonra değerlendiriliyor
    - ✓ CDAI
    - ✓ Hasta global (PGA)
    - ✓ Ağrı ve yorgunluk VAS (0-100)
    - ✓ Sabah tutukluğu
    - ✓ mHAQ (0–3); d
    - ✓ EuroQoL EQ-5D.
  - ✓1 yıl sonunda % 63.3 RTX te kalım







Morning stifness



den Broeder et al. Trials (2017) 18:403
DOI 10.1186/s13063-017-2134-x

STUDY PROTOCOL Open Access

Ultra-low dose of rituximab in rheumatoid arthritis: study protocol for a randomised controlled trial

Alfons A. den Broeder[1,2*], Lise M. Verhoef[1], Jaap Fransen[2], Rogier Thurlings[2], Bart J. F. van den Bemt[3,4], Steven Teerenstra[5], Nadine Boers[1], Nathan den Broeder[1] and Frank H. J. van den Hoogen[1,2]

Abstract

Background: A standard low-dosing schedule of rituximab (RTX; 2 × 500 mg or 1 × 1000 mg) is as effective for active rheumatoid arthritis (RA) as the registered dose (2 × 1000 mg). Moreover, several small uncontrolled studies suggest that even lower-dosed treatment with RTX also leads to good treatment response in patients with RA. Retreatment with such an 'ultra-low' dose RTX in patients who responded well to RTX induction treatment is of special interest, as long-term use of lower RTX doses may lead to shorter infusion duration, lower risk of adverse events and lower costs. However, the effect of ultra-low dose of RTX has not been investigated using a controlled trial of proper design and dimensions.

Methods/Design: REDO is an investigator driven six-month pragmatic, double-blind, randomised controlled non-inferiority trial on the effects of ultra-low-dose RTX (1 × 500 or 1 × 200 mg) compared to standard low dose (1 × 1000 mg) in RA patients who are being retreated with RTX. A total of 140 RA patients, having reached low disease activity (DAS28CRP < 2.9) after the previous RTX infusion and DAS28CRP < 3.5 at moment of retreatment, are randomised in a ratio of 1:2:2 to 1 × 1000 mg, 1 × 500 mg or 1 × 200 mg. The primary objective is testing non-inferiority of the ultra-low-dose vs. standard low-dose RTX, by comparing mean change in DAS28CRP from baseline to six months to the non-inferiority margin of 0.6. Secondary outcomes over the same period are: function; quality of life; safety; costs; and pharmacokinetics and dynamics as process measures.

Discussion: This study protocol shares characteristics of both early dose finding trials as well as late pragmatic clinical studies. Several choices in the design of this trial are described and possible consequences for RA treatment and expected biosimilar introduction are discussed.

Trial registration: Dutch Trial Register, NTR6117. Registered on 15 November 2016 (CMO NL57520.091.16, 8 November 2016)

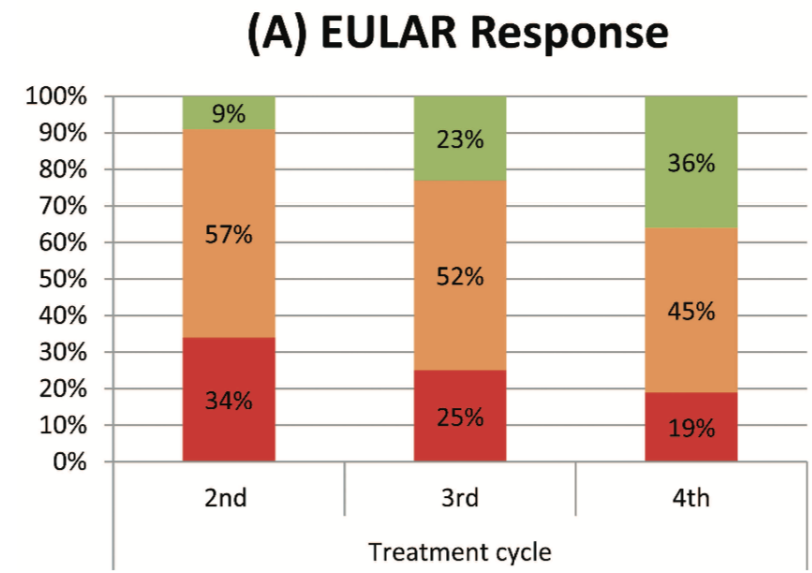
Keywords: Rheumatoid arthritis, Dose reduction, Rituximab, Low dose, Retreatment, Randomised controlled trial, Non-inferiority, Design, Decremental cost-effectiveness ratio (DCER)

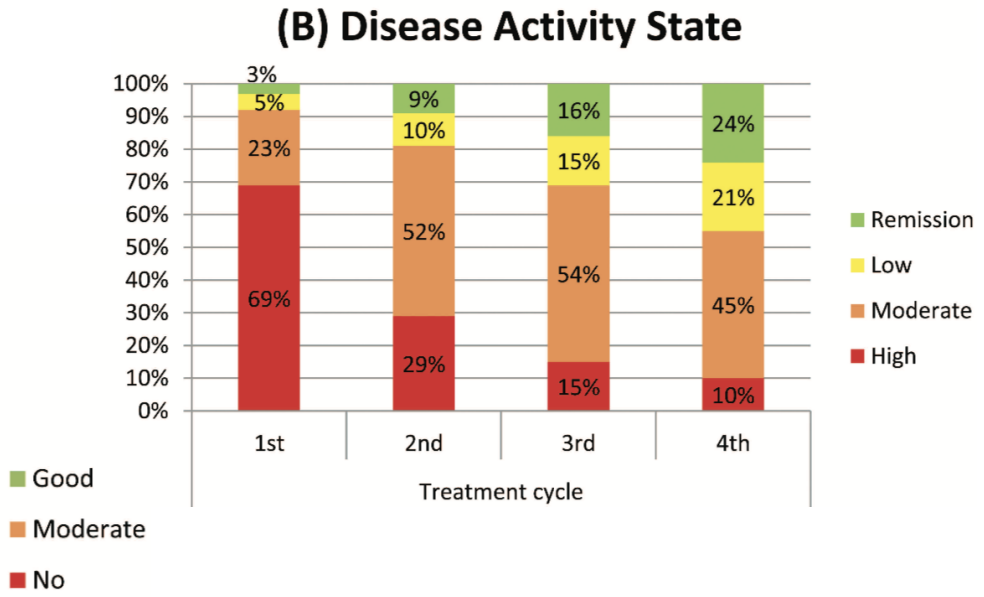
The Journal of Rheumatology

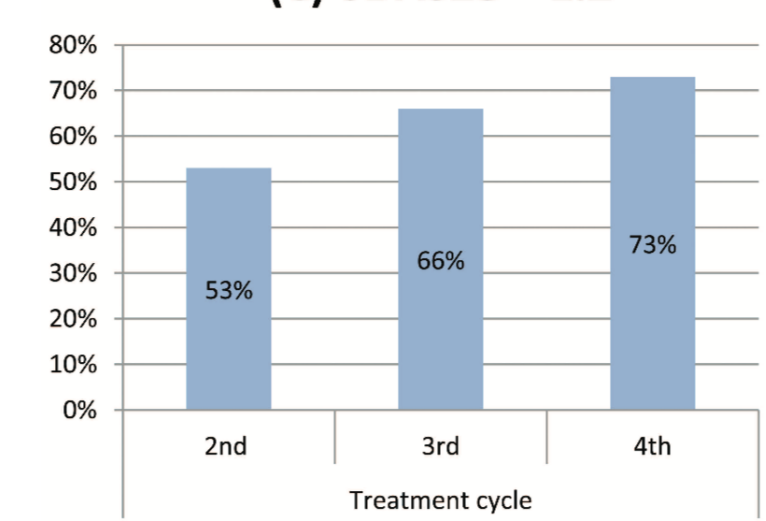
The Journal of Rheumatology

Rituximab Retreatment in Rheumatoid Arthritis in a Real-life Cohort: Data from the CERERRA Collaboration

Katerina Chatzidionysiou, Elisabeth Lie, Galina Lukina, Merete L. Hetland,



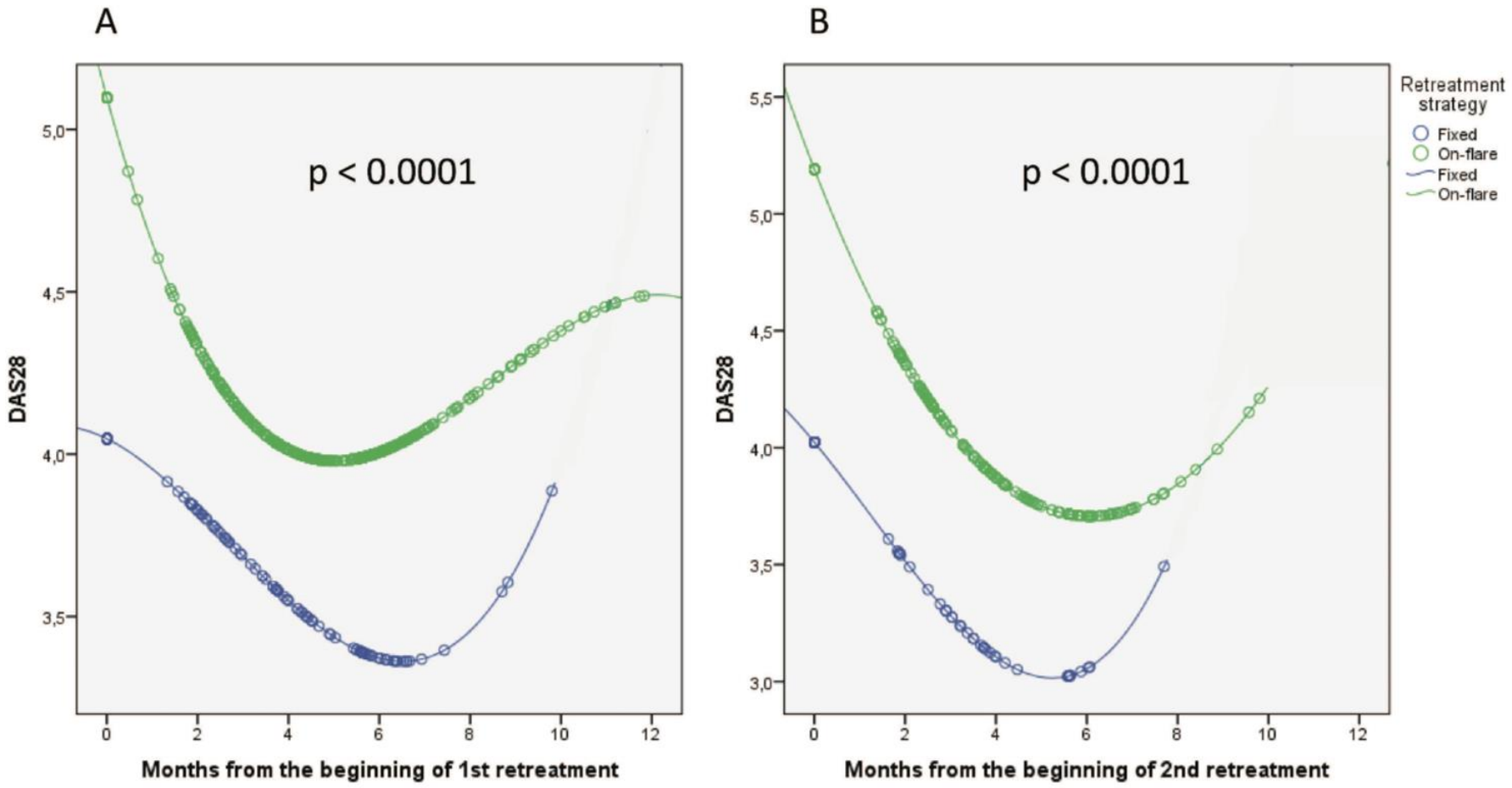




1530 hasta-En az 4 siklus RTX almış

1.analiz: Tekrarlayan tedavilerde yanıt değişimi

Tekrarlayan tedavilerde klinik iyileşmede artış



2. analiz:

Alevlenmelerde tedavi (n=616) vs. sabit aralıklı tedavi (n=184) farkı

Sabit aralıklı tedavi, alevlenme sonrası tedaviye göre daha etkili

DOI 10.1186/s13075-016-0951-z

RESEARCH ARTICLE Open Access

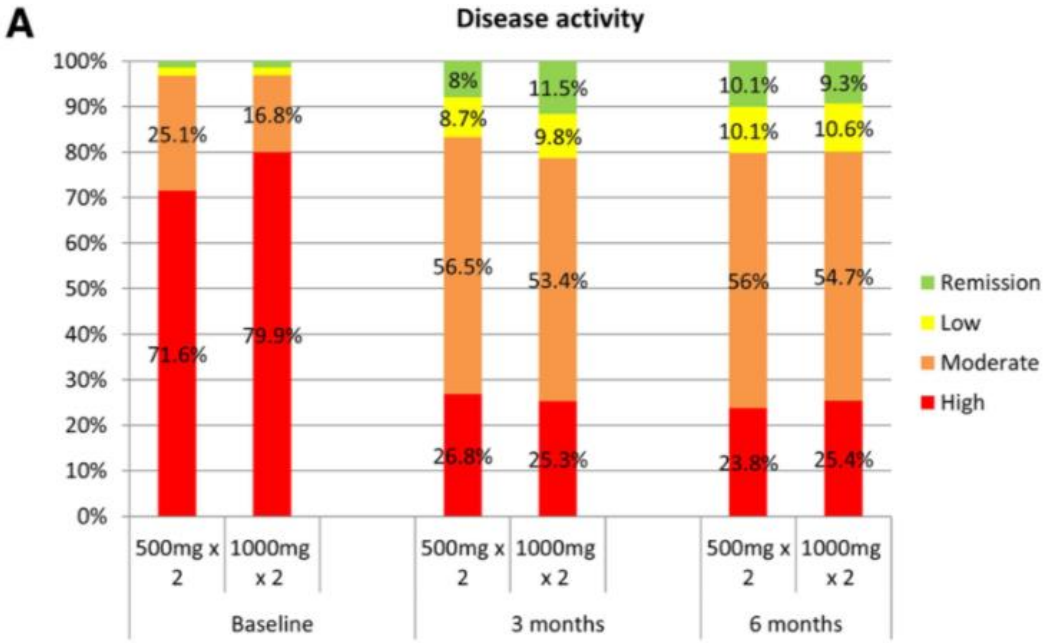
Effectiveness of two different doses of rituximab for the treatment of rheumatoid arthritis in an international cohort: data from the CERERRA collaboration

Katerina Chatzidionysiou[1*], Elisabeth Lie[2], Evgeny Nasonov[3], Galina Lukina[3], Merete Lund Hetland[4], Ulrik Tarp[5],

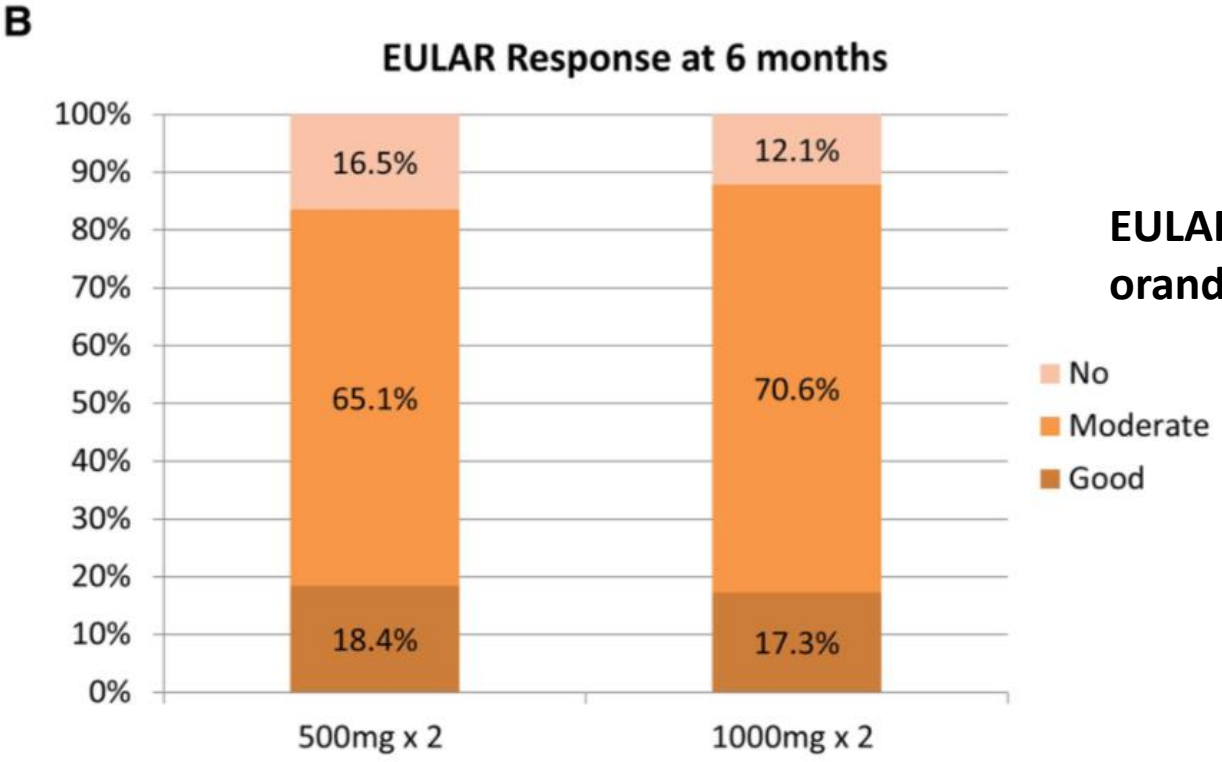
Table 1 Baseline demographics, disease and treatment characteristics of patients treated with rituximab 500 mg × 2 or 1000 mg × 2 for all patients in the cohort at baseline and for those with available response data (DAS28-ESR) at 6 months

	All patients			Patients with available response data at 6 months*		
	RTX 500 mg × 2 n = 248	RTX 1000 mg × 2 n = 2625	*P* value (*t* test, chi-square test)	RTX 500 mg × 2 n = 109	RTX 1000 mg × 2 n = 1385	*P* value (*t* test, chi-square test)
Sex,% female	83.9 % (248)	80.3 % (2,625)	0.17	88.1 % (109)	81.2 % (1,125)	0.08
Age, years	55.2 ± 15.8 (247)	52.6 ± 12.6 (2,615)	0.002	55.5 ± 15.1 (109)	51.1 ± 11.8 (1,380)	<0.0001
Disease duration, years	10.5 (5-18) (240)	8.1 (5-14) (2,360)	0.02	10 (5-16.8) (108)	7.5 (5.1-12) (1,329)	0.02
RF, % positive	81.7 % (241)	81.2 % (2,031)	0.84	83 % (106)	81.5 % (876)	0.7
Anti-CCP, % positive	71.3 % (101)	73.4 % (806)	0.64	68 % (50)	74.9 % (363)	0.29
Number of prior biologic agents	0 (0-1) (207)	1 (0-2) (2,560)	<0.0001	0 (0-1) (102)	1 (0-1) (1,371)	0.003
Anti-TNF-naive (%)	58 % (207)	37.5 % (2,560)	<0.0001	58.8 % (102)	37.1 % (1,371)	<0.0001
Number of prior DMARDs	2.6 ± 1.3 (126)	2.4 ± 1.4 (2,248)	0.04	2.7 ± 1.3 (55)	2.3 ± 1.1 (1,256)	0.02
Baseline DAS28-ESR	5.7 ± 1.3 (215)	6.1 ± 1.3 (2,069)	<0.0001	5.9 ± 1.3 (100)	6.3 ± 1.2 (1,344)	0.002
Baseline HAQ score	1.6 ± 0.7 (212)	1.7 ± 0.7 (1,584)	0.48	1.6 ± 0.7 (100)	1.8 ± 0.7 (695)	0.001
Concomitant medication:						
– Any DMARD	72.6 % (248)	83.1 % (2,625)	<0.0001	75.2 % (109)	87.5 % (1,385)	<0.0001
MTX	46.4 % (248)	63.4 % (2,625)	<0.0001	50.5 % (109)	75.1 % (1,385)	<0.0001
Glucocorticoids	65.7 % (248)	59.3 % (2,221)	0.06	71.6 % (109)	64.7 % (983)	0.15

The number of patients with available information for each variable is included in brackets. *RTX* rituximab, *RF* rheumatoid factor, *anti-CCP* anti-cyclic citrullinated peptide antibodies, *DMARDs* disease modifying anti-rheumatic drugs, *DAS28-ESR* Disease Activity Score based on 28 joints and erythrocyte sedimentation rate, *HAQ* health assessment questionnaire, *MTX* methotrexate



- Toplam 2,873 hasta,
- 2,625 (%91.4)----1000 mg × 2
- 248 (%8.6)----500 mg × 2
  - ✓ daha yaşlı,
  - ✓ hastalık süresi daha uzun,
  - ✓ öncesi DMARDs sayısı fazla,
  - ✓ öncesi biolojik sayısı az
  - ✓ bazal DAS28 daha düşük



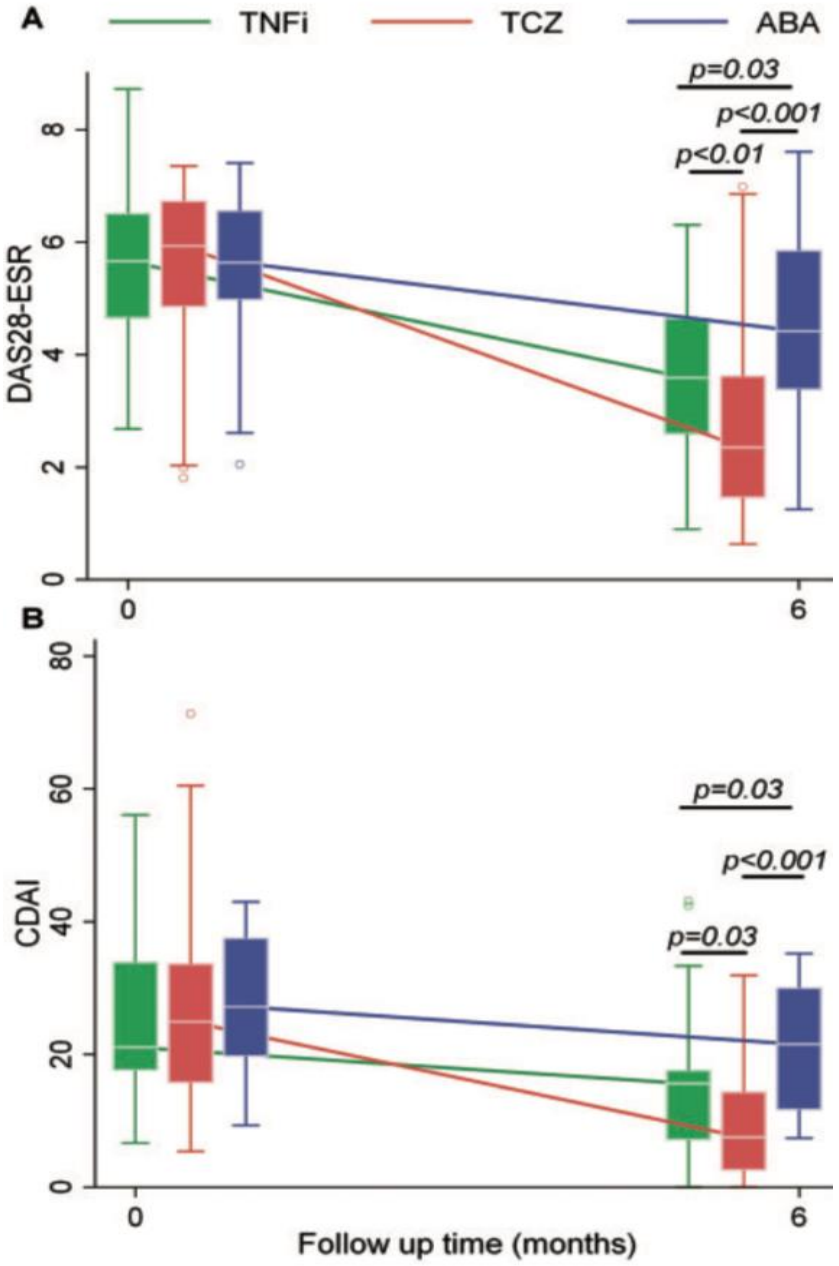
EULAR good response iki grupta benzer oranda 18.4 % vs. 17.3 %, (p = 0.36).

RHEUMATOLOGY
Original article
Rheumatology 2016;55:230–236
doi:10.1093/rheumatology/kev297
Advance Access publication 27 August 2015

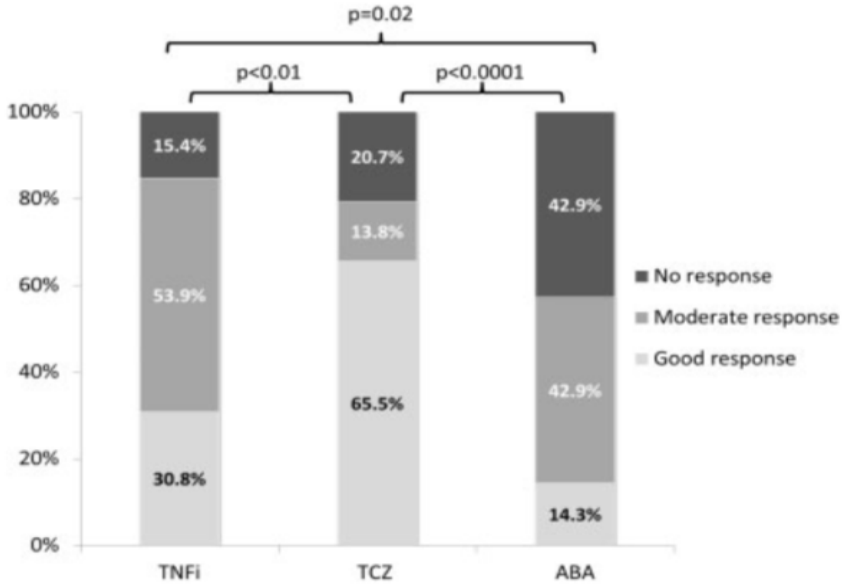
Rituximab done: what's next in rheumatoid arthritis? A European observational longitudinal study assessing the effectiveness of biologics after rituximab treatment in rheumatoid arthritis

Ulrich A. Walker[1,*], Veronika K. Jaeger[1,*], Katerina Chatzidionysiou[2],

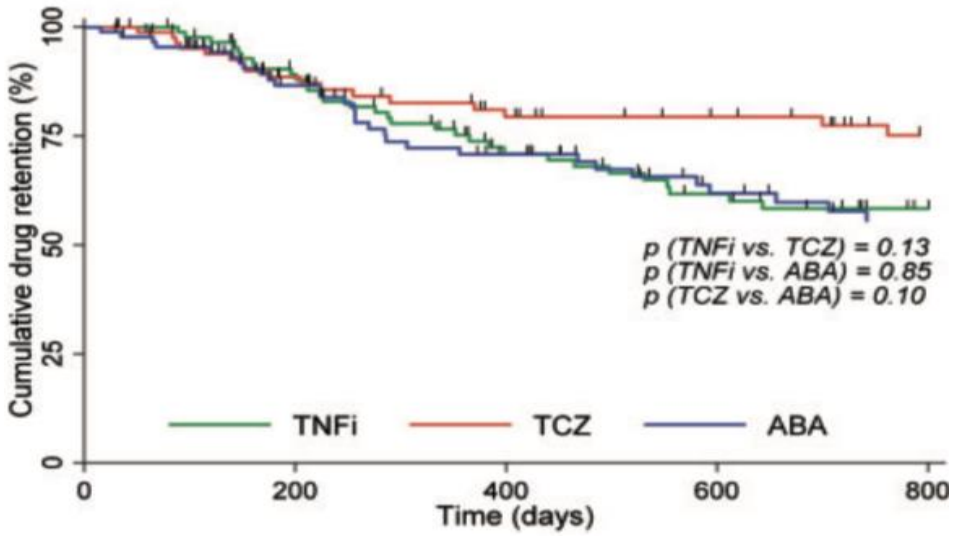
Characteristic	*n*	All patients (*n* = 265)	TNFi (*n* = 89)	ABA (*n* = 90)	TCZ (*n* = 86)	*P*-value
Female, %	265	57.0	61.8	57.8	51.2	0.36
Age, mean (S.D.), years	264	55.0 (12.2)	56.3 (12.3)	55.6 (12.0)	53.2 (12.2)	0.26
RA duration, median (IQR), years	257	12.0 (7.0–17.2)	12.7 (5.0–19.0)	11.7 (8.0–17.5)	12.0 (7.0–17.0)	0.91
RF positive, %	252	72.6	70.2	72.4	75.3	0.77
Anti-CCP positive, %	106	73.6	68.4	78.8	74.3	0.61
Number of bDMARDs prior to RTX, %						
0	219	11.4	13.5	17.6	2.8	0.08
1		25.6	29.7	21.6	25.4	
2		32.9	32.4	29.7	36.6	
⩾3		30.1	24.3	31.1	35.2	
Prednisone use, %	264	65.5	68.5	71.9	55.8	0.06
Prednisone dose, median (IQR), mg	264	7.0 (5.0–10.0)	6.3 (5.0–10.0)	7.5 (5.0–10.0)	5.0 (5.0–10.0)	0.50
MTX use, %	264	63.3	62.9	64.0	62.8	0.98
LEF use, %	264	11.0	12.4	12.4	8.1	0.59
Other sDMARD use, %	264	17.4	22.5	13.5	16.3	0.27
No concomitant sDMARD use, %	264	22.4	19.1	20.2	27.9	0.32
RTX stopped due to ineffectiveness, %	239	78.2	80.0	80.0	74.7	0.65



ıG. 2 EULAR responses at month 6 in the three treat-
ıent groups



ıG. 3 Kaplan–Meier curves for the time to discontinu-
ıion of TNF-α inhibitors, tocilizumab or abatacept



Joint Bone Spine 85 (2018) 219–226

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Original article

A multi-parameter response prediction model for rituximab in rheumatoid arthritis

Tamarah D. de Jong[a,1,*], Jérémie Sellam[b,1], Rabia Agca[a,c], Saskia Vosslamber[d], Birgit I. Witte[e], Michel Tsang-A-Sjoe[a], Elise Mantel[a], Johannes W. Bijlsma[a,c], Alexandre E. Voskuyl[a], Mike T. Nurmohamed[a,c], Cornelis L. Verweij[d,2,3], Xavier Mariette[f,2]

- Ra'da RTX tedavisine yanıtsızlık %30-40
- Yanıt 6 ay sonra değerlendiriliyor
- Yanıtı ön görebilmeye yönelik çalışma
  - Bazal aktivite, RF/CCP pozitifliği, yüksek ACPA titresi, daha önce anti TNF kullanım öyküsü ve sayısı
  - Memory B hüc., Plasmablast-CD4 T hüc., CCL19 düzeyi, IRG düzeyi
- İki bağımsız kohort (n: 93/133)
- IRG ekspresyonu ve RTX yanıtına bakılmış
- Artmış IRG ekspresyonu RTX yanıtsızlıkla ilgili?
  - Bu grupta TCZ ve AntiTNF yanıtı iyi

Joint Bone Spine 85 (2018) 219–226

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Original article

A multi-parameter response prediction model for rituximab in rheumatoid arthritis

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- Cevapsızlarda IFN skoru yüksek
- Prednisolon almayanlarda bu etki çok belirgin değil
- RTX Yanıtsızlığı
  - Düşük basal DAS28
  - Yüksek IFN skoru
  - DMARD kullanımı öyküsü
  - RF/CCP negatifliği

ile ilişkili

ARTICLE IN PRESS

Seminars in Arthritis and Rheumatism ∎ (2018) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Predictors of hypogammaglobulinemia during rituximab maintenance therapy in rheumatoid arthritis: A 12-year longitudinal multi-center study

G. Boleto, MD[a], J. Avouac, MD, PhD[a,b], J. Wipff, MD, PhD[a], M. Forien, MD[c], M. Dougados, MD, PhD[d], C. Roux, MD, PhD[d], A. Kahan, MD, PhD[a], P. Dieude[c], Y. Allanore, MD, PhD[a,b,*]

[a] Université Paris Descartes, Sorbonne Paris Cité, Service de Rhumatologie A, Hôpital Cochin, Paris, France
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[d] Université Paris Descartes, Sorbonne Paris Cité, INSERM U1153, Service de Rhumatologie B, Hôpital Cochin, Paris

- RTX tedavisi hipogamaglobulunemi ve infeksiyon riski oluşturabilir.
- Bu çalışmada uzun dönemde RTX tx alan hastalarda hipogamaglobulinemi bakılmış
- Çok merkezli, en az 30 ay RTX alan hastalar, n:134, ortalama izlem yaklaşık 80 ay
- Hipogamaglobulinemi gelişimi ort 64 ± 23 ay
- Hipogamaglobulinemi gelişenlerde ciddi infeksiyon riski yüksek (%26.1/6.3 P:0.003)
- Başlangıç gamaglobülini 8mg/dl altında olmak risk faktörü (HR:7.34)
- Konkomitant MTX kullanımı riski azaltıyor (HR:0.26)

International Reviews of Immunology

Risk factors predisposing to the development of hypogammaglobulinemia and infections post-Rituximab

Table 2. Risk factors for hypogammaglobulinemia post-Rituximab.

Disease	Risk factor	Outcome	Type of study (No. of patients)	Ref.
NHL	> 1 courses of RTX	Increased risk of hypogammaglobulinemia compared to patients treated with 1 course ($p = 0.002$)	Retrospective study (211)	[25]
	Previous exposure to purine analogues	Increased risk of hypogammaglobulinemia compared to patients without previous exposure ($p = 0.025$)		
NHL	>8 doses of RTX	Severe hypogammaglobulinemia in 50% of patients compared to 11.8% in patients treated with <8 doses ($p = 0.006$) associated with 3 times more infections	Case-control (136)	[26]
RA	RTX maintenance regimen	1.5% of the patients had hypogammaglobulinemia after the 1st course, 4.3% after the 2nd course, and 5.9% after the 3rd course	Prospective study (1039)	[27]
RA	Age at the administration of RTX	Older age was an independent predictor of u stained low IgG (HR 1.64 for every 10-years increased baseline age)	Case-control (2578)	[29]
SLE	Low IgM	Patients with serum IgM levels below 0.4 g/L at 12 months after RTX had significantly lower baseline levels than those with IgM within the normal range at1year follow-up ($p < 0.005$)	Retrospective study (57)	[77]
	MMF post-RTX	50% of the patients who developed hypo IgM were treated with MMF post-RTX		

NHL, Non-Hodgkin Lymphoma; RTX, Rituximab; RA, Reumatoid Arthritis; SLE, Systemic Lupus Erythematous; MMF, Mycophenolate Mofetil.

Table 3. Risk factors for the development of post-RTX infections.

Disease	Risk factor	Outcome	Type of study (No. of patients)	Ref.
NHL	RTX maintenance	Significant increase of the rates of infections ($p = 0.004$) and neutropenia ($p = 0.001$) in patients who had received RTX maintenance therapy compared with those who had not.	Meta-analysis (528)	[8]
NHL	IgG level and low IgG levels for >6 months	The development of severe hypogammaglobulinemia was associated with 3-fold increase of the risk of infections	Case-control (136)	[26]
NHL	1. Change in IgM after RTX administration 2. Duration of RTX therapy (days) 3. Use of G-CSF	Decrease of IgM levels after administration of RTX ($p = 0.009$), short duration of RTX therapy ($p = 0.021$) and administration of G-CSF ($p = 0.012$) were associated with a significant increase of the risk of infection	Retrospective study (63)	[38]
RA	Age at the administration of RTX	Older age was the only independent predictor of severe infection (HR = 1.43 for every 10-years increased baseline age, 95% CI = 1.24-1.63, $p < 0.001$).	Case-control (2578)	[29]
RA	1. Chronic lung disease and/or cardiac insufficiency 2. Extra-articular involvement 3. Low IgG level (< 6 g/l)	Chronic lung disease and/or cardiac insufficiency ($p = 0.01$), extraarticular involvement ($p = 0.009$), and low IgG level (<6 g/l) before initiation of RTX treatment ($p = 0.005$) were significantly associated with increased risk of a severe infection.	Prospective study (1303)	[33]
Multisystem Autoimmune Disease	Cumulative oral prednisolone exposure	Positive correlation ($r = 0.265$, $p < 0.001$) between cumulative oral prednisolone exposure and the occurrence of infection.	Retrospective study (177)	[28]
GPA	<u>For severe infections</u> 1) high cumulative dose of cyclophosphamide, 2) total CD4 at last visit 3) total Ig decline after 1 round <u>For chronic infections</u> 1) IgG level at nadir	Higher cumulative dose of cyclophosphamide ($p = 0.037$), lower CD4 cell levels at the last visit ($p = 0.045$) and a larger decrease of total Ig after the first RTX round ($p = 0.040$) were independently associated with severe infections. Low IgG at the nadir was the only independent risk factor for chronic infections ($p = 0.026$) by multivariate analysis	Retrospective study (35)	[41]

NHL, Non-Hodgkin Lymphoma; RTX, Rituximab; RA, Reumatoid Arthritis; GPA, granulomatosis with polyangiitis.

Pulmonary Pharmacology & Therapeutics 37 (2016) 24–29

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Effect of rituximab on pulmonary function in patients with rheumatoid arthritis

Daniel Franzen [a, *], Adrian Ciurea [b], Daniel J. Bratton [a], Christian F. Clarenbach [a], Tsogyal D. Latshang [a], Erich W. Russi [a], Diego Kyburz [c], Malcolm Kohler [a]

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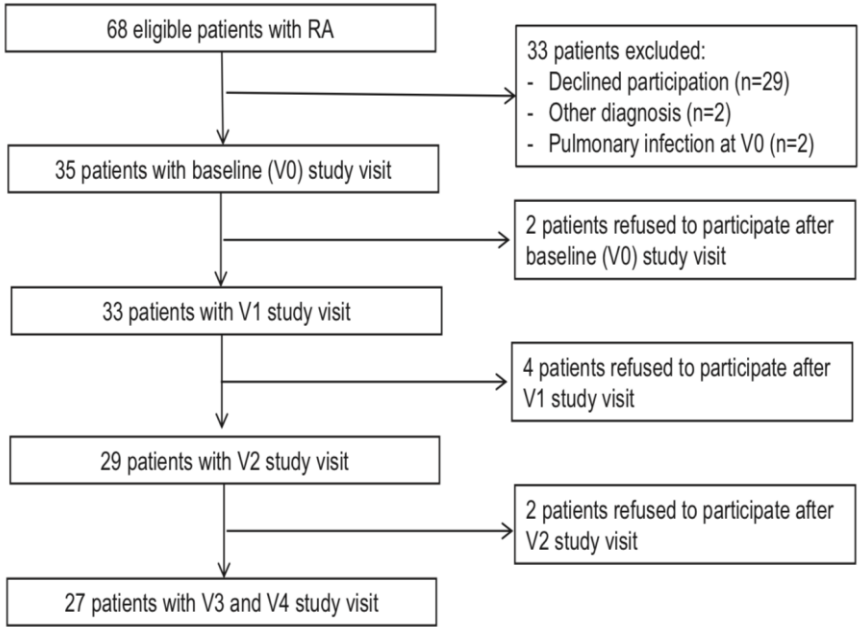


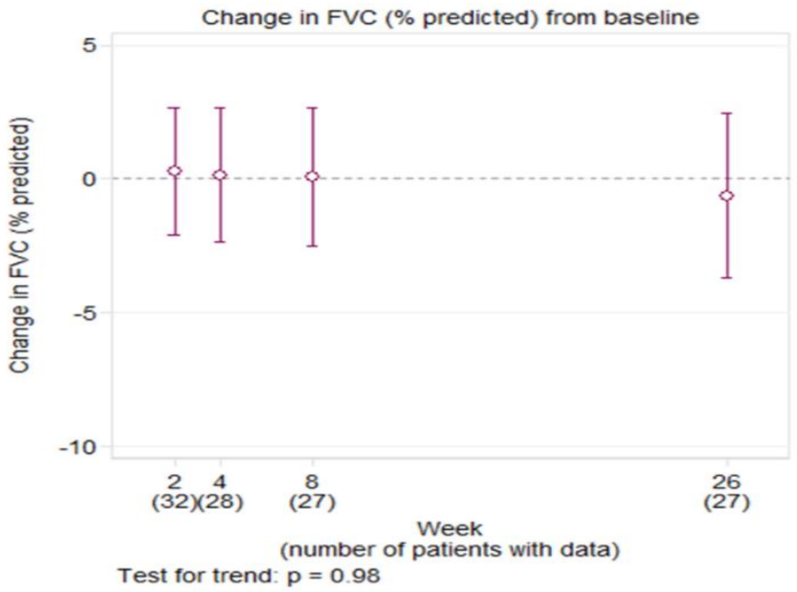
Baseline characteristics.

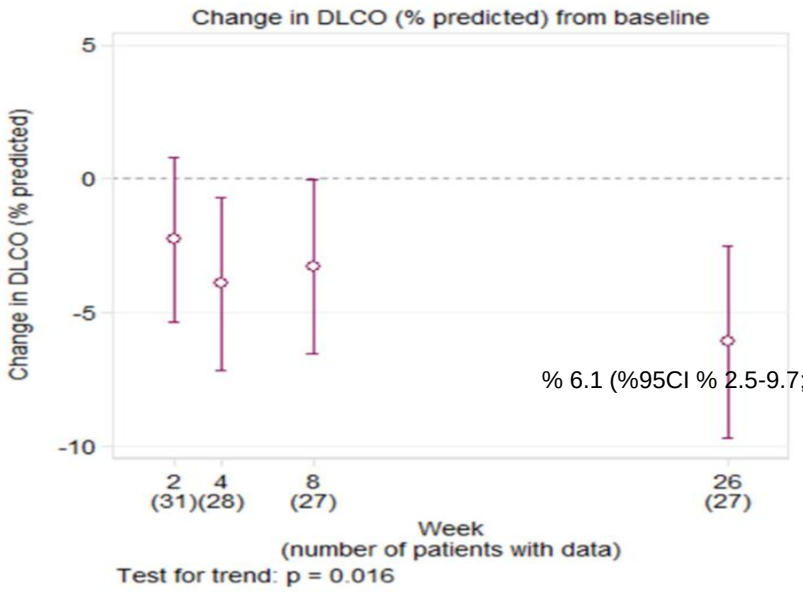
Age, mean (SD)	58.8 (11.7)
Male sex, n (%)	9 (27)
Body mass index [kg/m^2], median (IQR)	26 (23.5–30.5)
Active smoker, n (%)	17 (51)
- Pack-years, median (IQR)	20 (10–40)
Time from first diagnosis of RA [years], mean (SD)	10.1 (6.7)
First administration of rituximab, n (%)	7 (21)
Concurrent treatment for RA	
- Prednisone, n (%)/median mg per day (IQR)	22 (67)/5 (5–10)
- Methotrexate, n (%)/median mg per week (IQR)	14 (42)/17.5 (13.7–20.0)
- Leflunomid, n (%)	6 (18)
- Hydroxychloroquin, n (%)	5 (15)
Laboratory values	
- Blood sedimentation rate [mm/h], median (IQR)	15 (8.5–28.5)
- C-reactive protein [mg/dl], median (IQR)	3 (1–10.5)
- Leucocytes [x10^6/l], mean (SD)	7.9 (2.3)

N = 33. SD, standard deviation; IQR, interquartile range; RA, rheumatoid arthritis.

Bilinen akciğer tutulumları yok

- **FVC ve DLCO ; RTX öncesi ve RTX sonrası 2, 4, 8, and 26 haftalarda**
- **(FVC) ≥ % 10 veya DLCO ≥ %15 DLCO pulmonary toksite olarak tanımlandı**





% 6.1 (%95CI % 2.5-9.7; p =0.001)

- **26 hafta sonunda %22 hastada ≥ %15 DLCO azalma**
- **Hiç bir hastada semptom yok**
- **İlişkili risk faktörleri sigara, tekrarlayan ilaç inf., beraberinde steroid alımı**

RHEUMATOLOGY
Original article
Rheumatology 2017;56:1348–1357
doi:10.1093/rheumatology/kex072
Advance Access publication 24 April 2017

Effect of rituximab on the progression of rheumatoid arthritis–related interstitial lung disease: 10 years' experience at a single centre

Md Yuzaiful Md Yusof[1,2], Angela Kabia[1], Michael Darby[3], Giovanni Lettieri[1], Paul Beirne[4], Edward M. Vital[1,2], Shouvik Dass[1,2] and Paul Emery[1,2]

- **Gözlemsel çalışma –Tek merkez- RA-ILD**
- **FVC >%10 veya DLCO >%15 kötüleşme veya ILD'ye bağlı ölüm**

- **700 RA -RTX, 56 had RA-ILD (%8 prevelans)**
- **RTX sonrası yeni ILD 3/700 (%0.4 insidans)**
- **44/56 hastanın ILD değerlendirme verisi var**
- **RTXsonrası:**
  - 23/44 (%52) hasta stabil
  - 7/44 (%16) hastada iyileşme
  - 4/44 (32%) hastada ILD progresyon
  - 9/56 (%16) progresyona bağlı eksitus

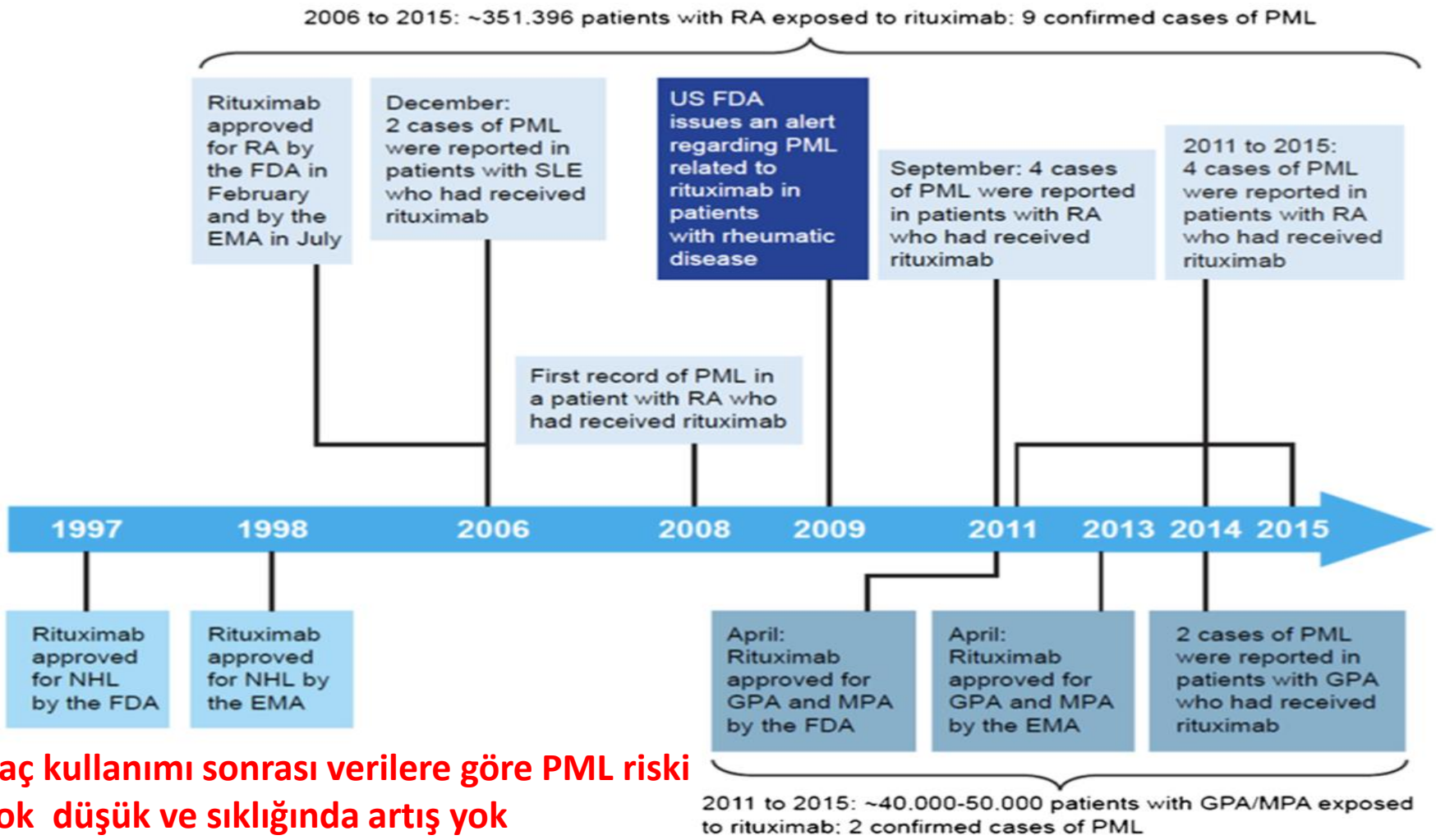
PreRTX DLCO<%46
UIP
Tx öncesi progressif giden ILD

Journal of NeuroVirology
https://doi.org/10.1007/s13365-018-0615-7

Progressive multifocal leukoencephalopathy in rituximab-treated rheumatic diseases: a rare event

Joseph R. Berger[1] · Vineeta Malik[2] · Stuart Lacey[3] · Paul Brunetta[4] · Patricia B. Lehane[3]

Received: 30 November 2017 / Revised: 24 January 2018 / Accepted: 29 January 2018
© Journal of NeuroVirology, Inc. 2018



İlaç kullanımı sonrası verilere göre PML riski çok düşük ve sıklığında artış yok

The Journal of Rheumatology

The Journal of Rheumatology

Low Risk of Hepatitis B Virus Reactivation in HBsAg-negative/Anti-HBc–positive Carriers Receiving Rituximab for Rheumatoid Arthritis: A Retrospective Multicenter Italian Study

Valentina Varisco, Mauro Viganò, Alberto Batticciotto, Pietro Lampertico, Antonio

306 patients with RA who underwent RTX-based treatment from August 2006 to Decembrer 2011 in 5 Italian outpatient rheumatological clinics

↓

216 patients (70%) had HBV markers available at start of RTX

↓

39 patients (18%) were HBsAg-negative/anti-HBc-positive

↓

33 HBsAg-negative/anti-HBc-positive patients did not undergo anti-HBV prophylaxis and were included in the study

- **33 RA (%73 kadın, medyan yaş 60) hastası Hastalar HBsAg-negatif/anti-HBc–pozitif**
- **%85 AntiHBs pozitif**
- **% 37 AntiHBe pozitif**
- **Profilaksi yok**
- **Medyan 3 (range 1–8) siklus RTX + ksDMARD,**
- **34 ay (range 0–80) izlem**

- **Serorevorziyon (HBsAg pozitifleşmesi) yok**
- **6/28 (%21) koruyucu anti-HBs düzeylerinde > 50% (2 hastada negatifleşme) düşme**
- **1(3%) hastada HBV DNA-positifleşmesi (LVM)**
- **14 hasta RTX kesildikten sonra medyan 18 ay (range 0–70) izlenmiş ve HBV reaktivasyonu gözlenmemiş**

Rheumatology 2017;56:661–663
doi:10.1093/rheumatology/kew493
Advance Access publication 29 January 2017

Pregnancy outcomes in women with rheumatoid arthritis ever treated with rituximab

Rates of live births were reassuring in women with RA exposed to rituximab before conception.

	Total population	Exposure to RTX within 6 months of conception	Exposure to RTX between 6 and 12 months before conception	Exposure to RTX >12 months before conception
Women, n[a]	23	8	7	13
Pregnancies, n	32	10	8	14
Number of RTX courses[b] before pregnancy, median (range)	2 (1–7)	2 (1–4)	2 (1–4)	2 (1–7)
Time between last dose of RTX and estimated date of conception, median (range), months	11 (1–89)	3 (1–5)	9 (6–11)	20 (12–89)
Known outcome, n	28	9	7	12
Live births, n (%)	21 (75)	6 (66)[c]	6 (86)	9 (75)
Miscarriages/stillbirths, n (%)	5 (18)	2 (22)	1 (14)	2 (17)
Termination, n (%)	2 (7)	1 (11)	0 (0)	1 (8)
Other anti-rheumatic drugs received at time of conception, n				
MTX	10	4	3	3
SSZ	7	2	1	4
CSs	5	2	1	2
HCQ	5	3	1	1
AZA	2	1	–	1
Ciclosporin	2	1	–	1
RTX restarted after delivery, n (%)	20 (63)	8 (80)	5 (63)	7 (50)
Time to RTX restart after delivery, median (range), months	4 (1–13)	4 (2–13)	1 (1–2)	4 (2–7)

RHEUMATOLOGY
Original article

Rheumatology 2016;55:2033–2039
doi:10.1093/rheumatology/kew314
Advance Access publication 22 August 2016

The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis

Lucía Silva-Fernández[1,2], Mark Lunt[1], Lianne Kearsley-Fleet[1], Kath D. Watson[1], William G. Dixon[1,3], Deborah P. M. Symmons[1] and Kimme L. Hyrich[1,3] on behalf of the British Society for Rheumatology Biologics Register (BSRBR) Control Centre Consortium

- **2001'den 2013'e kadar BSRBR'den ulusal kanser kayıtlarına bildirilen, daha önce bir malignitesi olan RA hastalarını kapsamaktadır.**
- **TNFi kohortunda, RTX kohortunda ve sentetikte DMARD kohortunda ilk malignite oranlarını karşılaştırılmış**

TABLE 1 Baseline patient characteristics

Characteristic	sDMARD (n = 159)	TNFi (n = 243)	Rituximab (n = 23)	P-value
Age, mean (S.D.), years	66.1 (10.0)	62.7 (9.5)	67.3 (9.9)	0.0005
Sex, female, n (%)	118 (74.2)	199 (81.9)	15 (65.2)	0.058
DAS28, mean (S.D.)	5.2 (1.2)	6.6 (1.1)	6.5 (0)	0.0001
HAQ score, mean (S.D.)	1.7 (0.7)	2.2 (0.5)	2.1 (0.3)	0.0001
Disease duration, median (IQR), years	8 (3–18)	12 (6–18)	14 (5–31)	0.0047
Prior sDMARDs, median (IQR)	2 (2–4)	4 (3–6)	3 (2–5)	0.0001
RF+, n (%)	100 (62.9)	156 (64.2)	17 (73.9)	0.588
Steroid use at baseline, n (%)	50 (31.5)	123 (50.6)	13 (56.5)	<0.001
Smoking, n (%)				0.050
Current	32 (20.4)	48 (19.9)	4 (17.4)	
Ex	78 (49.7)	87 (36.1)	11 (47.8)	
Never	47 (29.9)	106 (44.0)	8 (34.8)	
Entry year, n (%)				<0.001
Pre-2003	0	30 (12.4)	0	
2003	10 (6.3)	68 (28.0)	0	
2004	30 (18.9)	57 (23.5)	0	
2005	44 (27.7)	30 (12.4)	0	
2006 or after	75 (47.1)	58 (23.7)	23 (100)	
Prior malignancy, n (%)				0.014
Solid	133 (83.7)	213 (87.7)	19 (82.6)	
Lymphoproliferative	11 (6.9)	7 (2.9)	4 (17.4)	
Melanoma	15 (9.4)	23 (9.4)	0 (0)	
Time from most recent prior malignancy to registration				
Median (IQR), years	7.9 (3.0–13.3)	11.5 (5.8–17.6)	5.4 (3.0–9.2)	0.0001
>10 years preregistration, n (%)	59 (37.1)	138 (56.8)	4 (17.4)	<0.001

DAS28, Disease Activity Score 28; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor; sDMARDS, synthetic disease anti-rheumatic modifying drugs.

- **425 (malignitesi var)/18000 RA**
- **101 hasta yeni malignite gelişimi**
  - 33.3 events/1000 person-years (py) TNFi kohortu
  - 24.7 events/1000 py RTX kohortu
  - 53.8 events/1000 py sDMARD kohortu
- **Yaş ve cinsiyet düzeltilmiş hazard ratio (sDMARD koluyla karşılaştırıldığında)**
  - 0.55 (95% CI: 0.35, 0.86) TNFi kohortu
  - 0.43 (95% CI: 0.10, 1.80) RTX kohortu
- **Rekürrens oranı**
  - %17 sDMARDs kohortu
  - % 12.8TNFi kohortu
  - % 4.3RTX kohortu

Conclusions. Although numbers are still low, it seems that patients with RA and prior malignancy selected to receive either a TNFi or RTX in the UK do not have an increased risk of future incident malignancy.

Key words: rheumatoid arthritis, cancer, anti-TNF, rituximab, cohort study

Rheumatology key messages

- Patients with prior malignancy selected to receive biologics do not have an increased risk of incident malignancy.
- The time between past cancer and first biologic was shorter among rituximab than TNFi patients.
- It remains unknown whether biologics can be used safely in all patients with prior malignancy.

Received: 29 December 2016 | Accepted: 5 March 2017
DOI: 10.1111/jcpt.12522

CASE REPORT

WILEY Journal of Clinical Pharmacy and Therapeutics

Anterior ST-elevation myocardial infarction induced by rituximab infusion: A case report and review of the literature

K. Sharif MD[1,2] | A. Watad MD[1,2,3] | N. L. Bragazzi MD, PhD[4] | E. Asher MD, MHA[2,5] | A. Abu Much MD[1,2,5] | Y. Horowitz MD[1,2] | M. Lidar MD[2,6] | Y. Shoenfeld MD, FRCP, MaACR[2,3] | H. Amital MD, MHA[1,2,3]

TABLE 2 Summary of the patients described in the literature, experiencing myocardial infarction during the infusion of rituximab

Age	Sex	Infusion	Indication for rituximab	Type of MI	Risk factors for IHD	Outcome	References
60	Male	First	DLBCL	AWMI	Diabetes	Recovered	21
58	Male	First	CLL	N/A	Previous MI	Recovered	22
61	Male	First	BL	IWMI	N/A	Recovered	22
72	Male	First	BL	N/A	N/A	Died	22
65	Male	First	SLVL	IWMI	None	Recovered	23
62	Male	First	NHL	IWMI	N/A	Recovered	24
46	Male	Second	DLBCL	IWMI	Smoking: 25 pack-years	Recovered	25
70	Female	First and second	RA	ALWMI	Previous history of MI	Recovered	26
76	Female	Second	RA	AWMI	None	Recovered	26
52	Male	Third	MG	IWMI	None	Recovered	27
52	Female	24 h after first dose	ITP	IWMI	HTN, previous MI	Recovered	28
36	Male		PR3-ANCA-positive granulomatosis with polyangiitis	AWMI	Smoking: 20 pack-years, HTN, hypercholesterolaemia	Recovered	29
58	Male	Fifth	RA + Scleroderma	AWMI	HTN, smoking: 30 pack-years	Recovered	The current case

ORIGINAL ARTICLE
Immunology, Allergic Disorders & Rheumatology

JKMS

http://dx.doi.org/10.3346/jkms.2016.31.2.202 • J Korean Med Sci 2016; 31: 202-207

The Effects of Rituximab on Lipids, Arterial Stiffness, and Carotid Intima-Media Thickness in Rheumatoid Arthritis

- 55 RA-Kadın hasta, RTX tedavisi alan, bilinen KVH yok
- RTX öncesi ve 24 hf sonrası Lipid profili, DAS 28-ESR, CRP, RF, arteriyal sertlik (AS) ve karotis intima-media kalınlığı (cIMK) değerlendirİliyor
- RTX 24.hf EULAR cevaba göre 2 gruba ayrılıyor
  - ✓ 1) orta/iyi cevap n:41 (%75)
  - ✓ 2) cevap yok n:14 (%25)

Table 3. Dynamics of lipids profile, glucose level, systolic blood pressure, diastolic blood pressure, body mass index, and SCORE in patients with RA on rituximab therapy

Parameters	Group 1 (n = 41)		Group 2 (n = 14)	
	Baseline	After 6 mo	Baseline	After 6 mo
TC, mmol/L	5.64 ± 0.2	6.15 ± 0.2*	6.34 ± 0.5	6.73 ± 0.5
TC > 5 mmol/L, %	67	88	79	92
LDL-C, mmol/L	3.61 ± 0.2	3.73 ± 0.2	4.2 ± 0.5	4.2 ± 0.5
LDL-C > 3 mmol/L, %	74	85	74	85
TG, mmol/L	1.33 ± 0.1	1.36 ± 0.1	1.55 ± 0.2	1.59 ± 0.3
TG > 1.7 mmol/L, %	28	28	21	35
HDL-C, mmol/L	1.42 ± 0.1	1.73 ± 0.1*	1.44 ± 0.1	1.59 ± 0.1
HDL-C < 1.2 mmol/L, %	28	11*	28	14
Atherogenicity index	4.14 ± 0.2	3.78 ± 0.2*	4.52 ± 0.4	4.35 ± 0.4
Atherogenicity index > 4, %	55	31*	56	41
Fasting blood glucose, mmol/L	4.87 ± 0.1	4.96 ± 0.1	4.51 ± 0.1	5.1 ± 0.1
Fasting blood glucose > 6.0 mmol/L, %	5	2	0	0
SBP, mmHg	119 ± 2.8	119 ± 2.4	112 ± 2.8	125 ± 2.4
DBP, mmHg	74 ± 1.3	74 ± 1.3	71 ± 1.3	76 ± 1.3
BMI, kg/m^2	24.8 ± 0.6	24.5 ± 0.7	23.8 ± 1.3	22.6 ± 1.3
BMI < 20/20-25/ > 25 kg/m^2, %	52/31/17	50/33/17	43/36/21	30/40/40
SCORE, %	0.84 ± 0.2	0.83 ± 0.2	0.59 ± 0.2	0.61 ± 0.2

Data are presented as M ± m unless otherwise noted. *$P < 0.05$ before and after RTX treatment.

Table 4. Dynamics of arterial stiffness and carotid intima-media thickness in patients with RA on rituximab therapy

Parameters	Group 1 (n = 41)		Group 2 (n = 14)	
	Baseline	After 6 mo	Baseline	After 6 mo
SI, m/s	14.7 ± 0.9	9.9 ± 0.9*	12 ± 3	12 ± 3
RI, %	76.5 ± 3	67 ± 3	68 ± 2	75 ± 2
Stiffarteries, %	52	15*	28	36
IMTmean, mm	0.77 ± 0.03	0.69 ± 0.02*	0.77 ± 0.02	0.73 ± 0.03
IMTmax, mm	0.97 ± 0.03	0.87 ± 0.02*	0.93 ± 0.04	0.92 ± 0.04

Data are presented as M ± m unless otherwise noted. *$P < 0.05$ before and after rituximab therapy. SI, stiffness index; RI, reflection index; IMT, intima-media thickness.

RTX tedavisi TC %9 / HDL-C %14 arttırıyor ve aterojenik indeksi %57 / stiffnes indeksi %54 ve reflection indeksi %24 azaltıyor.
24. Haftada cIMT max ta %9 azalma gözlenmiş.
CRP, ESR, RF ve DAS28 parametrelerinde yanıt veren grup1 de anlamlı azalma. Grup 2 de azalma görülmemiş.

RHEUMATOLOGY

Rheumatology 2018;57:134–139
doi:10.1093/rheumatology/kex403
Advance Access publication 23 October 2017

Concise report

Serious infusion-related reaction after rituximab, abatacept and tocilizumab in rheumatoid arthritis: prospective registry data

Jean-Hugues Salmon[1,2], Jeanne-Marie Perotin[3,4], Jacques Morel[5],

- Fransız Romatoloji derneğinin, bağımsız , prospektif 3 kayıt-kütüğü verisi inceleniyor
  - autoimmunity and rituximab (AIR) (n= 1948)
  - Orencia (abatacept) and RA (ORA) (n=827)
  - Registry RoAcTEmra (tocilizumab) (REGATE) (n=1370)
- SIRRs infüzyon anında ya da ilk 24 saat içinde gelişen infüzyonu kesilmesi veya tedavi değişikliği gerektiren durum
- Hasta özellikleri elektronik veri tabanından elde edilmiş

- Toplam 4145 hasta, SIRRs 100 hastada görülmüş
  - RTX kohort 56 hasta (2.8% ve ya 0.7/100 hasta-yılı)
  - Abatasept kohort 15 hasta (1.5% ve ya 0.6/100 hasta-yılı)
  - Tosilizumab kohortu 24 (1.9% ve ya 1/100 hasta-yılı)
- Fatal SIRR olmamış
- multivariate analizde yüksek riskle ilşkili faktörler
  - ✓ anti-CCP pozitifliği (odds ratio = 2.5; 95% CI: 1.01, 6.17).
  - ✓ Konkomitan sentetik DMARD olmaması (odds ratio = 1.67; 95% CI: 1.00, 2.86).

Sellam *et al. Arthritis Research & Therapy* (2016) 18:294
DOI 10.1186/s13075-016-1190-z

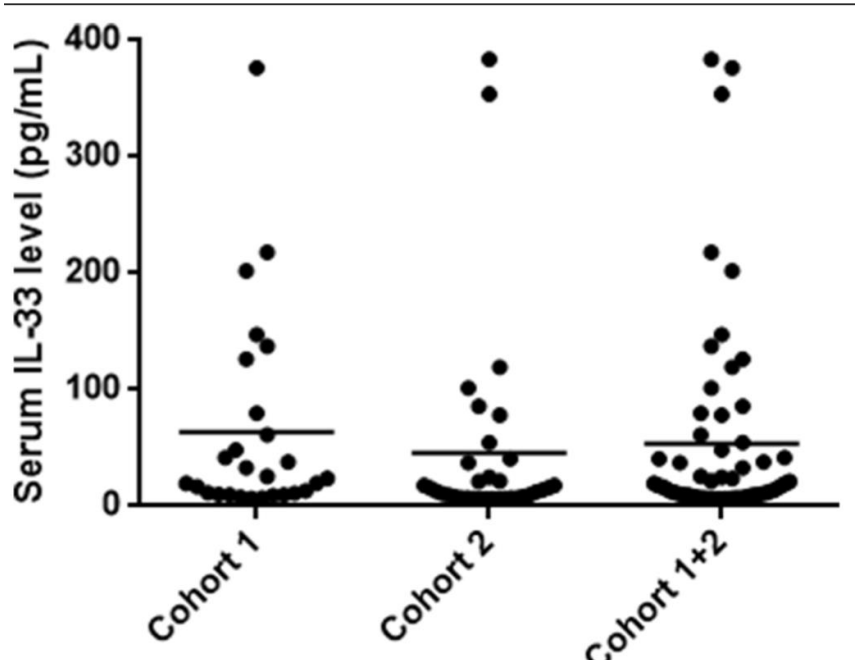
Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

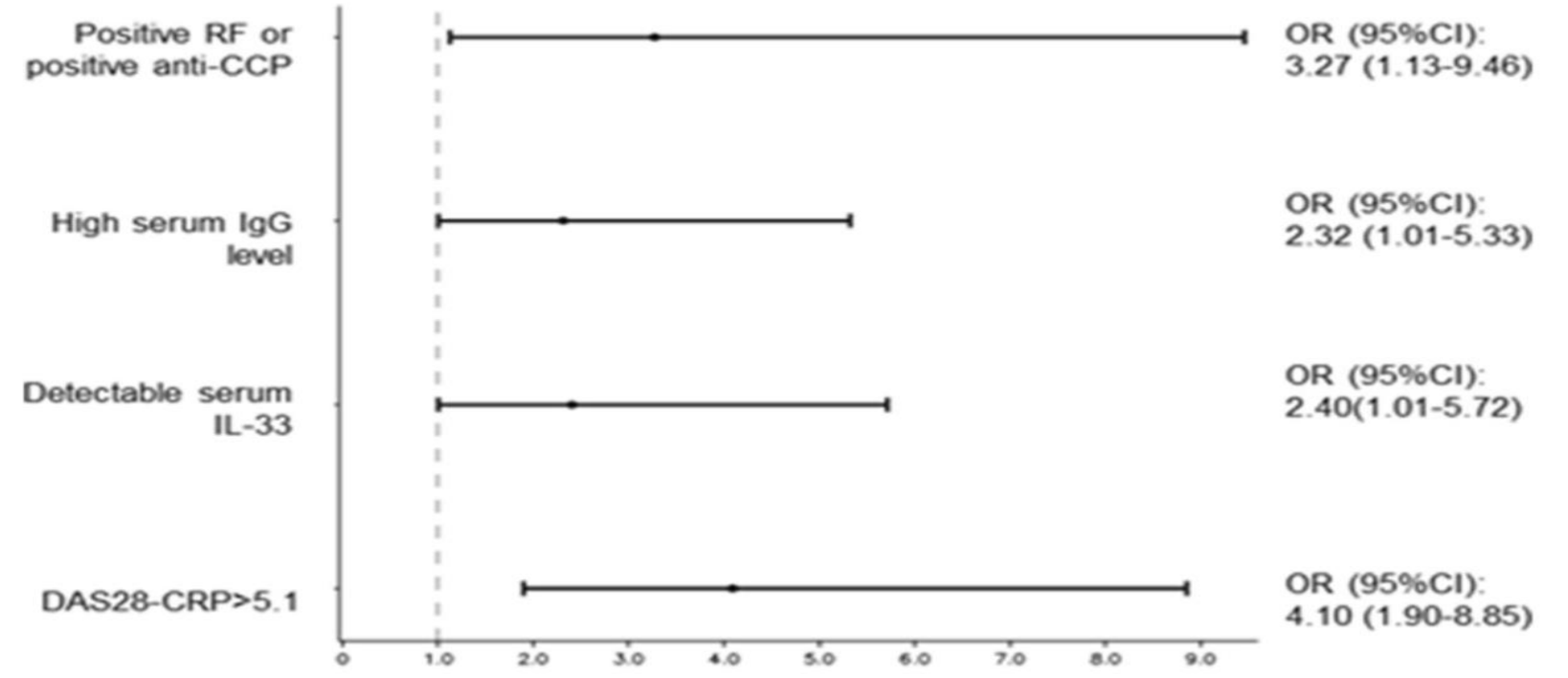
Serum IL-33, a new marker predicting response to rituximab in rheumatoid arthritis

Jérémie Sellam[1,10*†], Elodie Rivière[2†], Alice Courties[1], Paul-Olivier Rouzaire[3], Barbara Tolusso[4], Edward M. Vital[5],

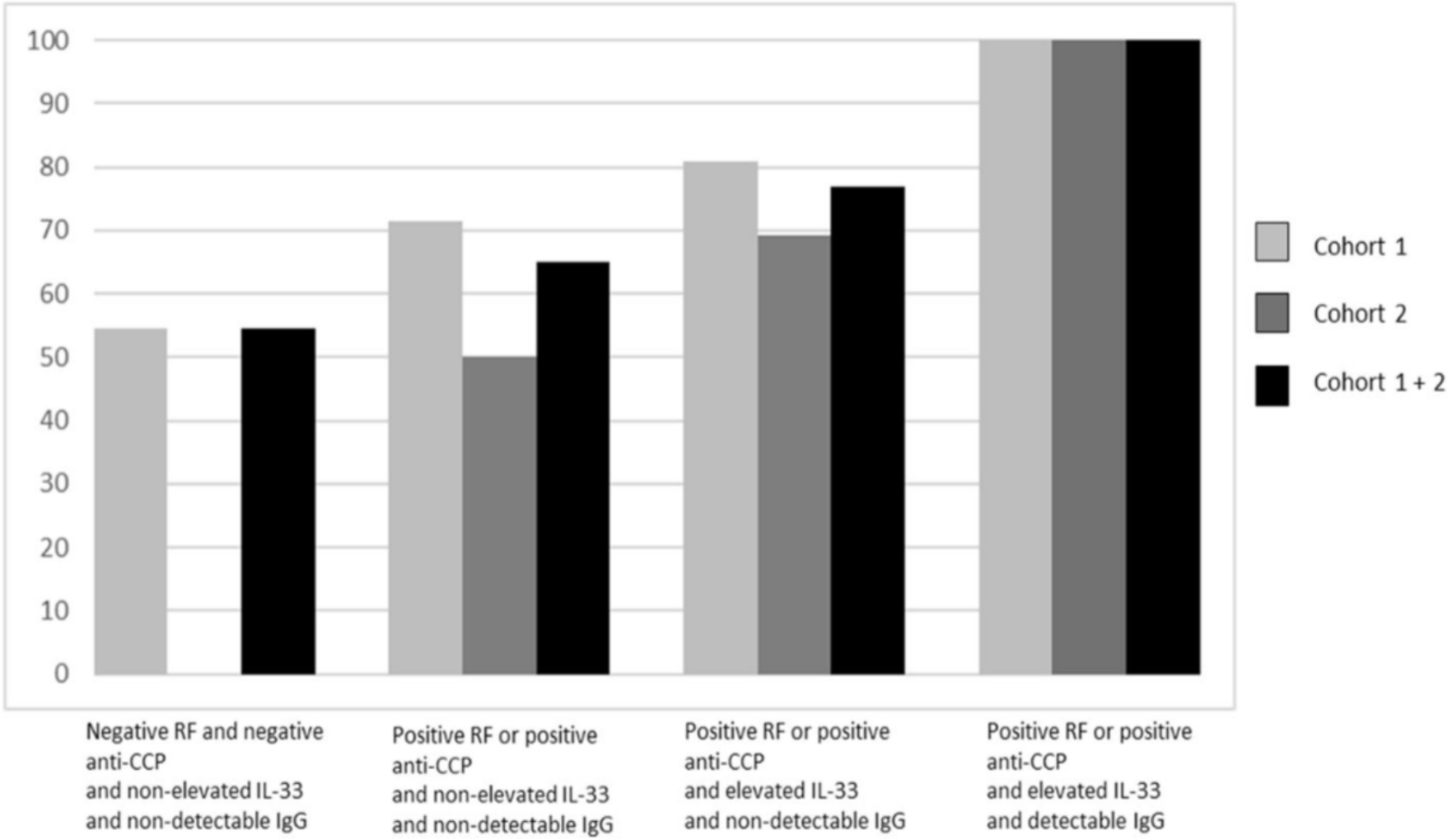
- Serum IL 33, CCP, RF, IgG düzeyleri RTX öncesi ölçülüyor
- Kohort 1- gözlemsel çalışma; 111 RA ilk siklus 2 g RTX
- Kohort 2- (rutin pratik) benzer tedavi takvimi; 74 RA
- 24. hf . EULAR response ve Univariate and multivariate analizle ilişkili faktörler



24. Hf EULAR yanıtı kohort1:%76, 2:%73



24.Hf EULAR response



Lavielle *et al. Arthritis Research & Therapy* (2016) 18:253
DOI 10.1186/s13075-016-1152-5

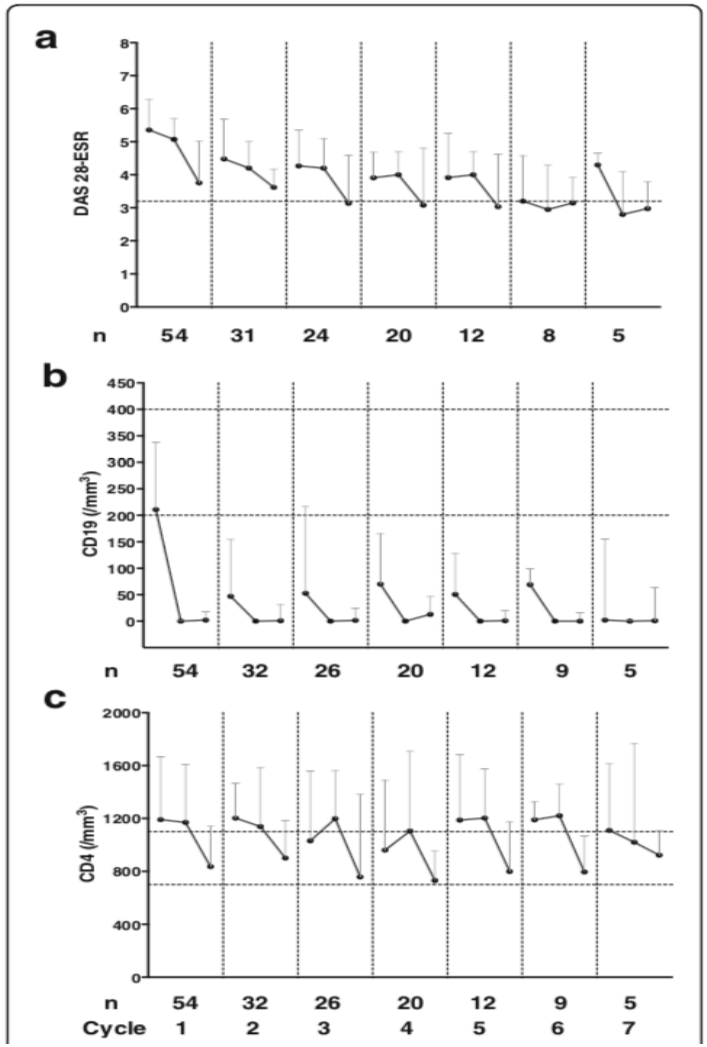
Arthritis Research & Therapy

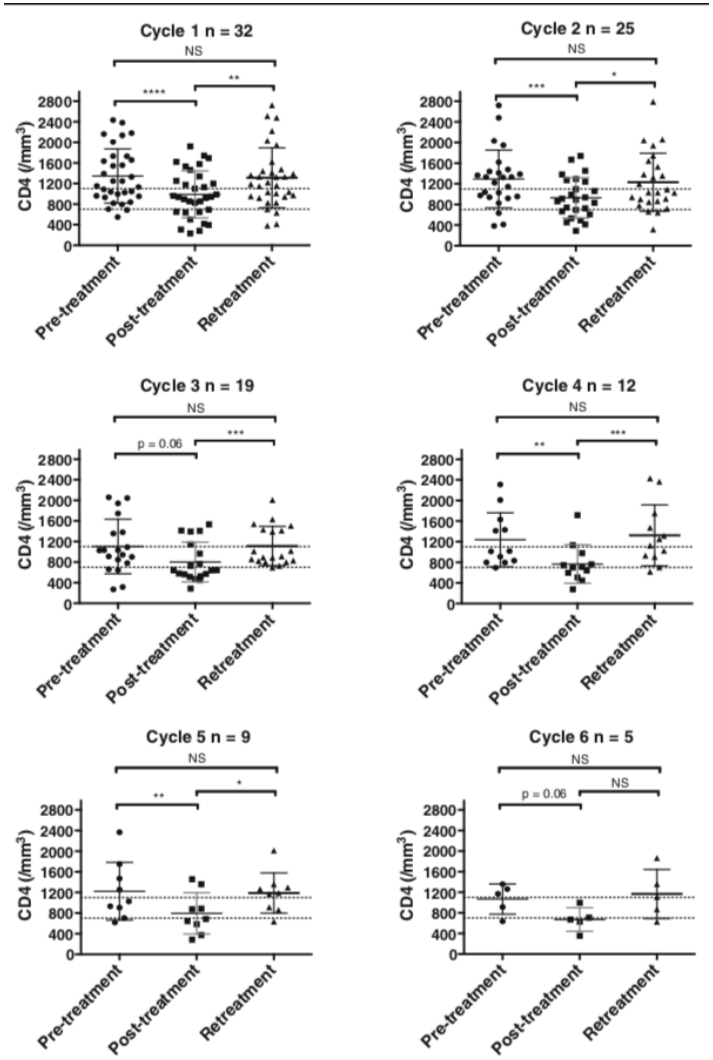
RESEARCH ARTICLE Open Access

Repeated decrease of CD4+ T-cell counts in patients with rheumatoid arthritis over multiple cycles of rituximab treatment

Matthieu Lavielle[1,2,3†], Denis Mulleman[1,2,4*†], Philippe Goupille[1,2], Clément Bahuaud[1,2], Hsueh Cheng Sung[1], Hervé Watier[1,3] and Gilles Thibault[1,3]

- **RTX sonrası periferik kanda CD4+ T-cell deplesyonu**
  - **RTX cevap yok---- CD4+ T-cell azalma yok ?**
  - **Tekrarlayan RTX inf. CD4+ T-cell ve klinik cevap üzerine etkisi**
- **Haz. 2007-2013 RTX başlanan 54 RA hastası**
  - **Lenfosit fenotipleme ve klinik değerlendirme her siklusun 0., 3., 6., aylarda yapılıyor**





CD4 + T hücre sayısı RTX cevabı ve tekrar eden tedaviyi planlamada anlamlı

Drug Design, Development and Therapy

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REVIEW

Current perspective on rituximab in rheumatic diseases

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
3 October 2017
Number of times this article has been viewed

Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial

Won Seog Kim, Christian Buske, Michinori Ogura, Wojciech Jurczak, Juan-Manuel Sancho, Edvard Zhavrid, Jin Seok Kim, José-Ángel Hernández-Rivas, Aliaksandr Prokharau, Mariana Vasilica, Rajinish Nagarkar, Dzhelil Osmanov, Larry W Kwak, Sang Joon Lee, Sung Young Lee, Yun Ju Bae, Bertrand Coiffier

Lancet Haematol 2017; 4: e362–73

Clinical and epidemiological research

OPEN ACCESS

CONCISE REPORT

A multicentre randomised controlled trial to compare the pharmacokinetics, efficacy and safety of CT-P10 and innovator rituximab in patients with rheumatoid arthritis

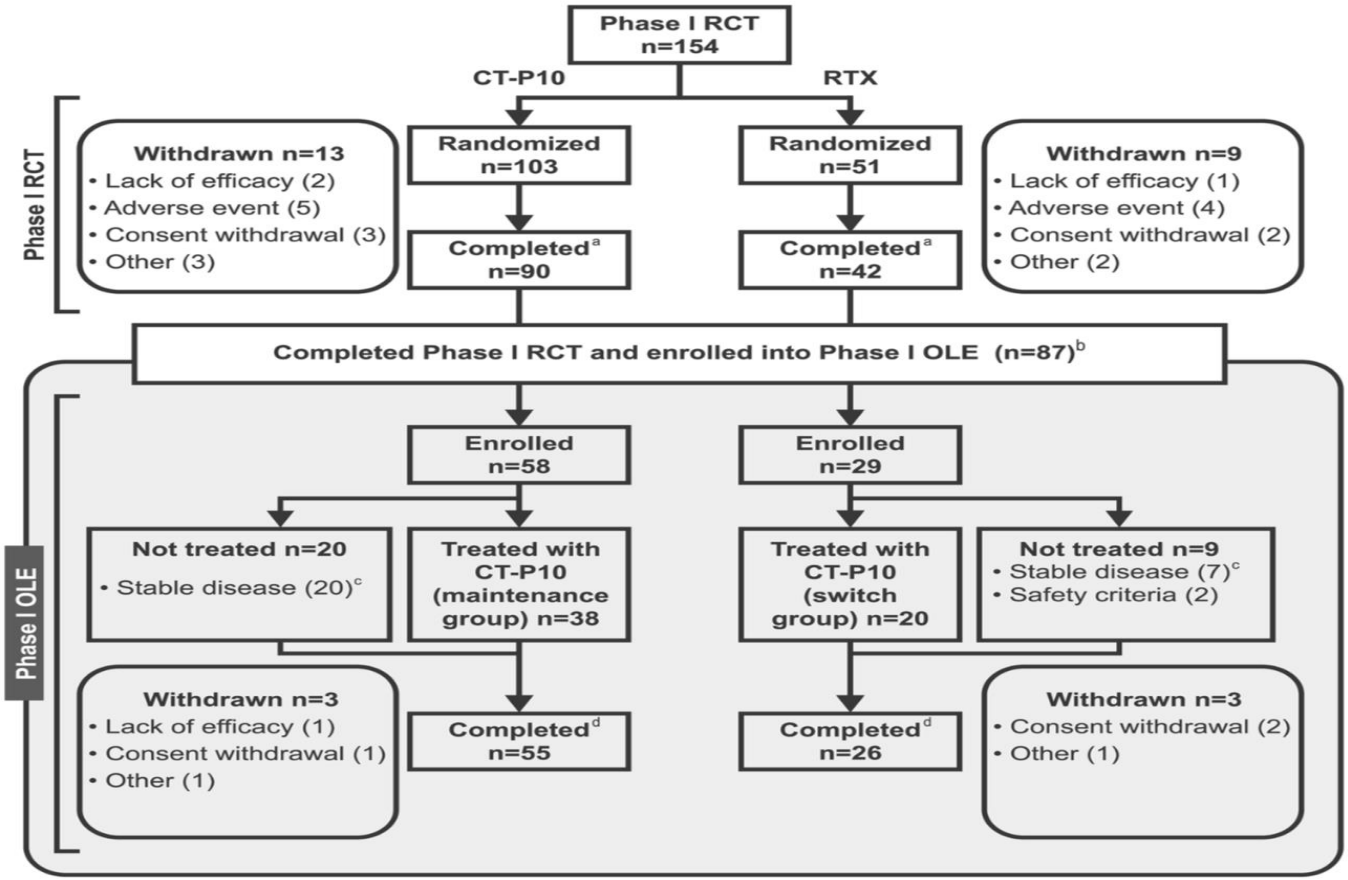
Dae Hyun Yoo,[1] Chang-Hee Suh,[2] Seung Cheol Shim,[3] Slawomir Jeka,[4] Francisco Fidencio Cons-Molina,[5] Pawel Hrycaj,[6] Piotr Wiland,[7] Eun Young Lee,[8] Francisco G Medina-Rodriguez,[9] Pavel Shesternya,[10] Sebastiao Radominski,[11] Marina Stanislav,[12] Volodymyr Kovalenko,[13] Dong Hyuk Sheen,[14] Leysan Myasoutova,[15] Mie Jin Lim,[16] Jung-Yoon Choe,[17] Sang Joon Lee,[18] Sung Young Lee,[18] Taek Sang Kwon,[18] Won Park[16]

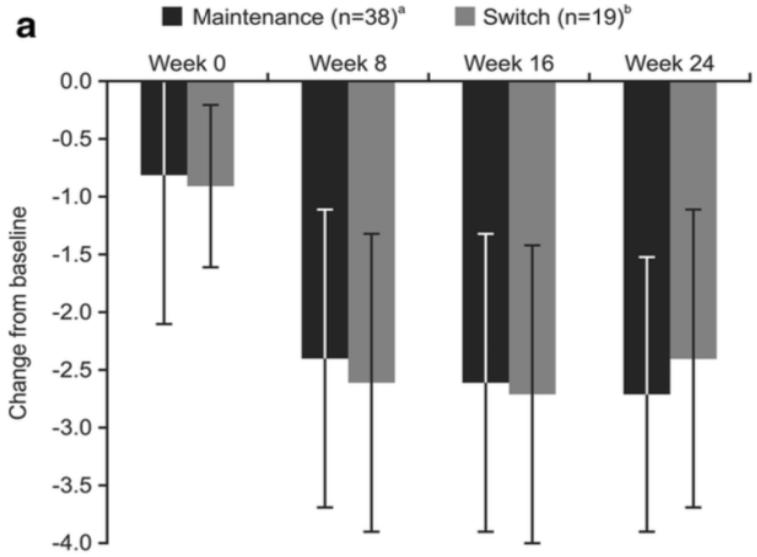
BioDrugs (2017) 31:369–377
DOI 10.1007/s40259-017-0233-6

ORIGINAL RESEARCH ARTICLE

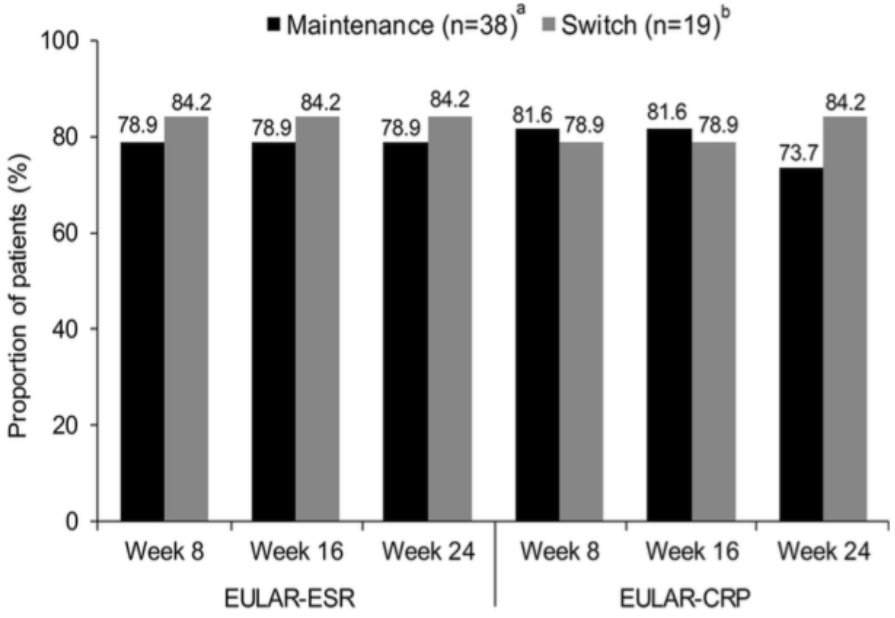
Efficacy and Safety of Switching from Innovator Rituximab to Biosimilar CT-P10 Compared with Continued Treatment with CT-P10: Results of a 56-Week Open-Label Study in Patients with Rheumatoid Arthritis

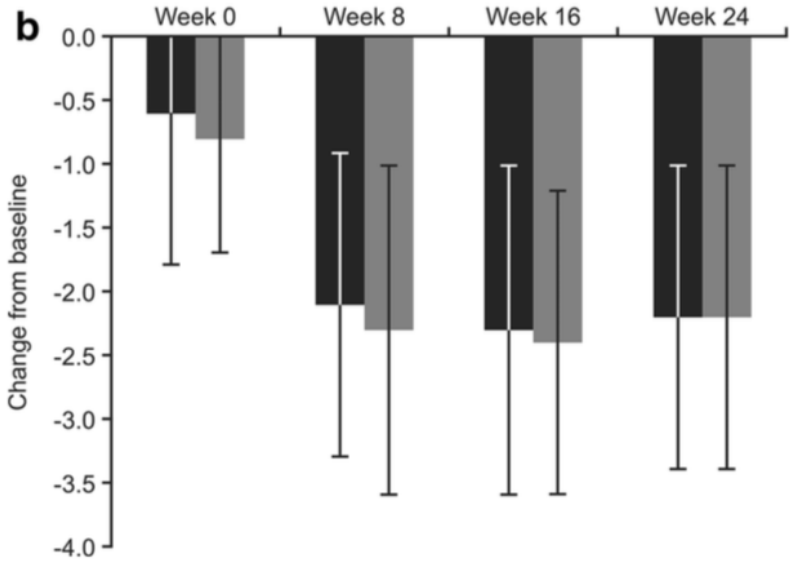
Won Park[1] · Chang-Hee Suh[2] · Seung Cheol Shim[3] · Francisco Fidencio Cons Molina[4] ·





a DAS28-ESR ort. değişim





b DAS28-CRP ort. değişim

Table 3 Summary of adverse events in patients who received study treatment (CT-P10) during the open-label extension study (safety population)

Adverse events	Number of patients with ≤1 event (%)	
	Maintenance group[a] ($n = 38$)	Switch group[b] ($n = 20$)
Any adverse event	9 (23.7)	4 (20.0)
Any serious adverse event	1 (2.6)	1 (5.0)
Spinal osteoarthritis	1 (2.6)	1 (5.0)
Infusion-related reaction	1 (2.6)	1 (5.0)
Infection	3 (7.9)	2 (10.0)
Gastroenteritis	1 (2.6)	0
Respiratory tract infection	1 (2.6)	0
Upper respiratory tract infection	2 (5.3)	1 (5.0)
Urinary tract infection	2 (5.3)	1 (5.0)
Malignancy or lymphoma	0	0
Study drug discontinuation due to adverse event	0	0

ELSEVIER

Optimising B-cell depletion in autoimmune disease: is obinutuzumab the answer?

Venkat Reddy[1], Lekh N. Dahal[2], Mark S. Cragg[2,3] and Maria Leandro[1,3]

[1] Centre for Rheumatology and Bloomsbury Rheumatology Unit, Division of Medicine, Rayne Building, 4th Floor, 5 University Street, WC1E 6JF, London, UK
[2] Antibody and Vaccine Group, Cancer Sciences Unit, University of Southampton Faculty of Medicine, Southampton, UK

Other anti-CD20 mAbs in clinical trials or in clinical use in RA and SLE.

CD20 mAb	Type	Disease	Sponsor	Stage of trial	Results	Refs
Ocrelizumab	I	RA	Genentech/Roche/Biogen	Phase III	Primary endpoints met (48 weeks, dose-dependent serious infections)	[44]
Ofatumumab	I	RA	Genmab	Phase III	Primary endpoints met (24 weeks, no serious adverse events)	[99]
TRU015	I[a]	RA	Trubion/Pfizer	Phase I & II	Primary endpoints not met	[100,101]
Ocrelizumab	I	SLE (LN)	Genentech/Roche/Biogen	Phase III	Not superior to placebo	[102]
Obinutuzumab (GA101)	II	SLE	Glycart/Roche	Phase I/II	Commenced November 2015	
Ocaratuzuamab (AME133v, LY2469298)	I	RA	Mentrik Biotech/Eli Lilly	Phase I	N/A	

[a] TRU015 is a single-chain Fv generated from 2H7 linked to human IgG1 but devoid of CH1 and CL domains. The original mAb was type I [40].*Abbreviations:* RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; LN, lupus nephritis; N/A, not available.

Rheumatol Int (2017) 37:1053–1064
DOI 10.1007/s00296-017-3675-8

Rheumatology
INTERNATIONAL

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SAFETY AND PHARMACOVIGILLANCE

Safety and efficacy of ocrelizumab in rheumatoid arthritis patients with an inadequate response to methotrexate or tumor necrosis factor inhibitors: a systematic review and meta-analysis

Abdelrahman Ibrahim Abushouk[1,2,3] · Hussien Ahmed[3,4] · Ammar Ismail[2,3,5] · Ahmed Elmaraezy[2,3,5] · Ahmed Said Badr[3,6,7] · Mohamed Gadelkarim[3,8] · Mohammed Elnenny[3,5]

Table 1 Summary of the methodology and findings of included studies

Study ID	Study design	Sample size (*n*)	Population	Intervention	Control	Main finding
Genovese et al. 2008	Phase I/II, randomized, blinded, placebo-controlled, dose-ranging study	237	Patients with moderate to severe RA	Phase I: OCR 20 mg + MTX. Phase II: OCR 10, 50, 200, 500 or 1000 mg + MTX	Placebo + MTX	OCR was effective in inhibiting the progression of joint damage and improving RA signs and Symptoms. The rate of serious infections was higher for OCR 500 mg than OCR 200 mg or Placebo
Rigby et al. 2012	Phase III, randomized, double-blind, placebo-controlled, parallel-group study	1015	Patients with active RA with an inadequate response to MTX 7.5–25 mg/week	OCR 200 or 500 gm + MTX	Placebo + MTX	OCR was effective in inhibiting the progression of joint damage. The rate of serious infections was higher for OCR 500 mg than OCR 200 mg or Placebo
Harigai et al. 2012	Phase II, double-blinded, placebo-controlled, multicenter study	152	RA patients with an inadequate response to MTX 6–8 mg/week	OCR 50, 200, or 500 mg + MTX	Placebo + MTX	The results suggest inappropriate benefit-risk balance of OCR in this patient population
Tak et al. 2012	Phase III, randomized, double-blind, placebo-controlled, Parallel-Group Trial	840	Patients with active RA	OCR 200 mg or OCR 500 mg + MTX or (LEF) Leflunomide	Placebo + MTX or LEF	The rate of serious infections was higher for both OCR doses than Placebo

LEF leflunomide, *MTX* methotrexate, *OCR* ocrelizumab, *RA* rheumatoid arthritis

4 rkç, n:2230 24 haftada OCE+Mtx vs Mtx + pl dan anlamlı etkin p<0.00001

Table 1. Study Designs, Demographic and Baseline Characteristics.

	OFA110635	OFA110634	OFA111752
Study design			
Type of study	Phase III	Phase III	Phase II extension
Planned duration	24-week DB period; 120-week OL period[a]; Safety FU up to 2 yrs.	24-week DB period; 120-week OL period[a]; Safety FU up to 2 yrs.	130-week OL period[a]; Safety FU up to 2 yrs.
Number of sites	36	41	17
Geographic locations	Europe, South America, Australia	Europe, South America, East Asia	Europe, North America
Key inclusion and exclusion criteria			
Age	≥18 years	≥18 years	≥18 years
Gender	Male or non-pregnant female	Male or non-pregnant female	Male or non-pregnant female
RA disease characteristics	Active RA for ≥6 months; ≥8 swollen and ≥8 tender joints (of 66/68 assessed); CRP ≥1.0 mg/dl or ESR ≥22 mm/h; DAS28-ESR ≥3.2	Active RA for ≥6 months; ≥8 swollen and ≥8 tender joints (of 66/68 assessed); CRP ≥1.0 mg/dl or ESR ≥22 mm/h; DAS28-ESR ≥3.2	Active RA for ≥6 months; ≥3 swollen and ≥3 tender joints (of 28 assessed); DAS28-ESR ≥3.2
Previous RA therapy	Biologic naive and failed treatment with MTX	Failed treatment with TNF antagonist	Failed treatment with at least one DMARD
MTX therapy at study entry	Required (7.5–25 mg/week for ≥12 weeks and at stable dose for ≥4 weeks)	Required (7.5–25 mg/week for ≥12 weeks and at stable dose for ≥4 weeks)	Not required (if on MTX had to be on 7.5–25 mg/week for ≥12 weeks, and at stable dose for ≥4 weeks)
IgG	≥LLN	≥LLN	≥LLN
Demographic and baseline characteristics			
N	260	169	92
Mean (SD) age, years	52.7 (11.39)	53.5 (12.67)	52.9 (10.73)
Female, n (%)	214 (82)	140 (83)	84 (91)
Race, n (%)			
White	253 (97)	135 (80)	92 (100)
Asian	1 (<1)	32 (19)	0
African American/ African	1 (<1)	0	0
Other	5 (2)	2 (1)	0
Mean (SD) disease duration, yrs	8.51 (8.174)	12.8 (9.08)	12.7 (8.95)
Concomitant MTX, n (%)	260 (100)	169 (100)	87 (95)
RF positive, n (%)	219 (84)	124 (73)	79 (86)
Anti-CCP positive, n (%)	224 (86)	137 (81)	80 (87)
Mean (SD) swollen joint count	15.9 (7.14)	16.4 (7.90)	11.2 (5.22)
Mean (SD) tender joint count	27.6 (13.00)	28.0 (13.29)	15.5 (6.45)
Mean (SD) DAS28-CRP	5.7 (0.80)	5.9 (0.96)	5.8 (0.95)

PLOS | ONE

RESEARCH ARTICLE

Safety of Repeated Open-Label Treatment Courses of Intravenous Ofatumumab, a Human Anti-CD20 Monoclonal Antibody, in Rheumatoid Arthritis: Results from Three Clinical Trials

Emilia Quattrocchi[1]*, Mikkel Østergaard[2], Peter C. Taylor[3], Ronald F. van Vollenhoven[4], Myron Chu[5], Stephen Mallett[6], Hayley Perry[6], Regina Kurrasch[5]

- **483 hasta (n=243, 148 ve 92 sırasıyla; OFA110635, OFA110634 ve OFA111752), 7 siklus iv ofatumumab**
- **Yanetki; %93 (226/243), %91 (134/148) ve %76 (70/92) sırasıyla**
- **Ciddi yanetki; %18 (44/243), %20 (30/148) ve %12 (11/92) sırasıyla**
- **Ciddi enfeksiyon; %3 (8/243), %5 (7/ 148) ve %1 (1/92) sırasıyla**
- **En sık yanetki ilk infüzyonda oluşan allerjik reaksiyon (%48–79)**
- **Ciddi infüzyon ilişkili reaksiyonlar (<%1 [1/243], %5 [8/148], ve %1 [1/92] sırasıyla)**
- **2 hasta eksitus (fulminant hepatitis B virus infeksiyonu ve interstitial akciğer hastalığı).**

Clinical Therapeutics/Volume 38, Number 6, 2016

Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Properties of SBI-087, a CD20-Directed B-cell Depleting Agent: Phase 1 Dose Escalating Studies in Patients With Either Mild Rheumatoid Arthritis or Systemic Lupus

Stanley Cohen, MD[1]; Megan Clowse, MD, MPH[2]; Patricia Pardo, MD[3]; Indranil Bhattacharya, PhD[4]; Sandeep Menon, PhD[4]; Ian Gourley, MD[5]; and Annette Diehl, MPH[6]

[1]Metroplex Clinical Research Center, Dallas, Texas; [2]Department of Medicine, Division of Rheumatology and Immunology, Duke University, Durham, North Carolina; [3]Miami Research Associates, South Miami, Florida; [4]Pfizer Inc, Cambridge, Massachusetts; [5]Janssen, Spring House, Pennsylvania; and [6]Pfizer Inc, Collegeville, Pennsylvania

- SMIP; small molecular immunopharmaceutical protein
- RA ve SLE'de faz1
- IV ve sc uygulanan formları var
- MA düşük infüzyon reaksiyonu az
- İnflamatuvar dokuya penetrasyonu daha iyi
- B hücre düşürücü etkisi iyi ve uzun
- RA'da etki SLE'den daha belirgin

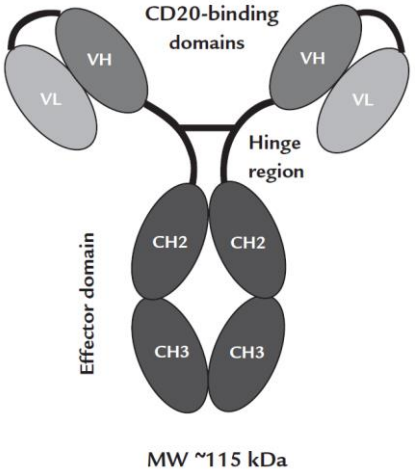

Figure A1. SMIP SBI-087 molecule. CH = constant domain, heavy chain; MW = molecular weight; SMIP = small modular immunopharmaceutical; VH = variable domain, heavy chain; VL = variable domain, light chain.

The Journal of Rheumatology

The Journal of Rheumatology

Safety and Efficacy of SBI-087, a Subcutaneous Agent for B Cell Depletion, in Patients with Active Rheumatoid Arthritis: Results from a Phase II Randomized, Double-blind, Placebo-controlled Study

Nemanja Damjanov, Malgorzata Tlustochowicz, Jacob Aelion, Maria Greenwald, Annette Diehl, Indranil Bhattacharya, Elena Peeva, Sandeep Menon and Ian Gourley

DOI: 10.3899/jrheum.160146
http://www.jrheum.org/content/early/2016/09/27/jrheum.160146

- 210 hasta randomize edilmiş
- 1-15. gün sc enjeksiyon
- 8. haftada ACR %20, DAS28 CRP, PGA, PtGA, HAQ-DI
- CD19+B hücre sayımı
- SBI-087 CD 20 hücreleri azaltıyor
- Tüm sonlanımlarda etki iyi
- YE sıklığı ilaçta %61.5 Plasebo %55

TEŞEKKÜRLER