14ο Πανελλήνιο Συνέδριο Επιστημονικής Εταιρεία για
τη Μυοσκελετική Υγεία – Ρόδος 2022

«Έρπητας Ζωστήρας σε ρευματολογικούς ασθενείς υπό ανοσοτροποποίηση»

Ευάγγελος Θεοδώρου, Ρευματολόγος,

Επιμελητής 251 ΓΝΑ, Αθήνα

Σύγκρουση συμφερόντων

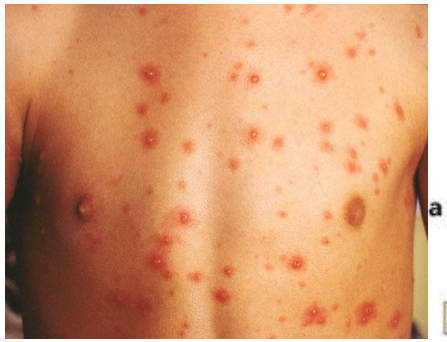
Δεν υπάρχει σύγκρουση συμφερόντων για τη συγκεκριμένη παρουσίαση

Ροή της παρουσίασης

Εισαγωγή	**Έρπητας Ζωστήρας (ΕΖ)** **Ποιος ο λόγος για τη σημερινή παρουσίαση;**
Γενικά στοιχεία	**Ασθενείς με ρευματικά νοσήματα και εμφάνιση ΕΖ**
Ρευματοειδής αρθρίτιδα	**Κίνδυνος εμφάνισης, Θεραπευτική κατηγορία, αλλαγή θεραπείας**
Ψωριασική αρθρίτιδα – Αγκυλοποιητική Σπονδυλίτιδα	**Κίνδυνος εμφάνισης, επιπολασμός, παράγοντες κινδύνου**
ΣΕΛ	**Κίνδυνος εμφάνισης, οργανοειδική νόσος, θεραπευτική κατηγορία**
Ανοσοτροποποίηση – Εμβολιασμός	**Εμβολιασμός υπό ανοσοκαταστολή**
Επίλογος	**Σκέψεις για τον σύγχρονο ρευματολόγο**

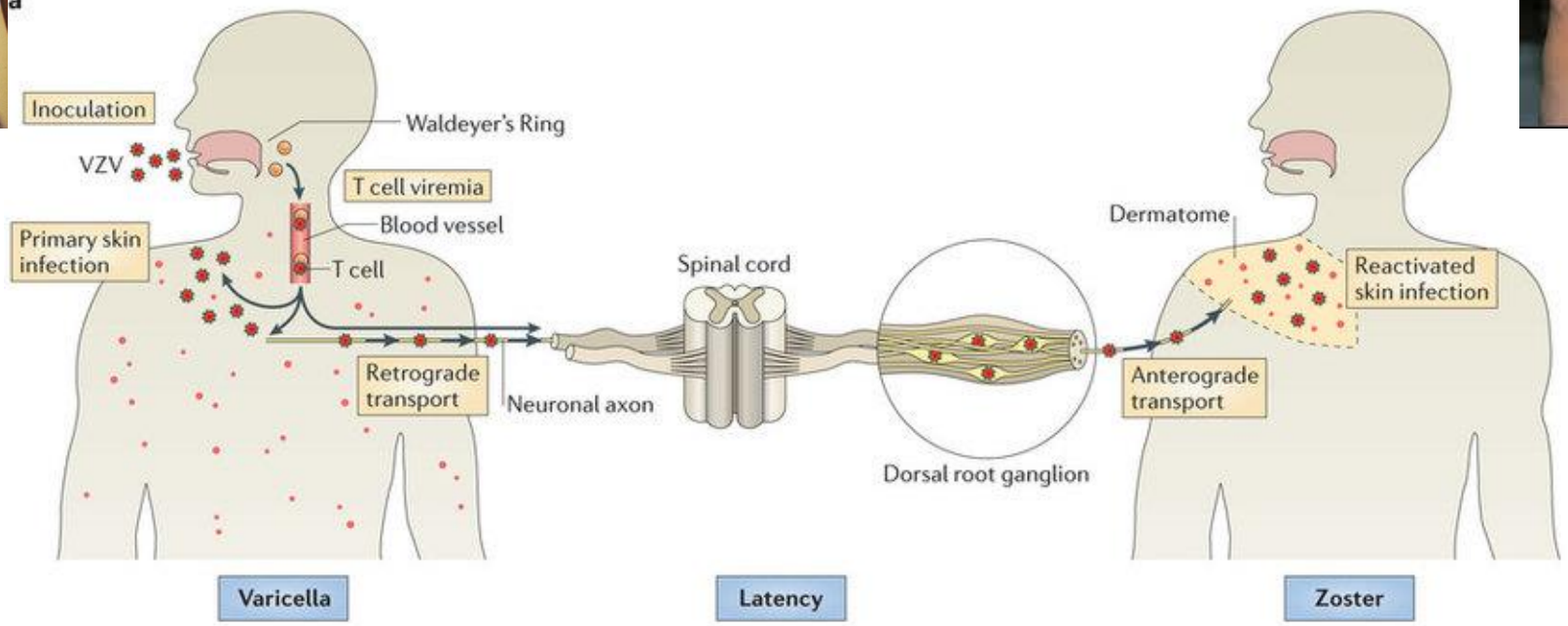
VZV : Ένας ιός - δύο νόσοι

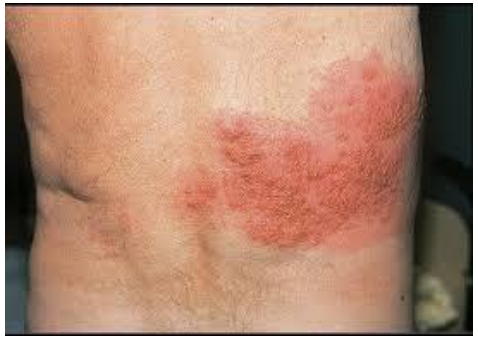
- Varicella-zoster virus (VZV) - alphaherpesviridae
  - ✓ Varicella (chickenpox) – Ανεμευλογιά (πρωτογενής νόσος)
  - ✓ Herpes zoster (shingles) – Έρπητας Ζωστήρας (αναζωπύρωση)



Ανεμευλογιά
Παιδική ηλικία

Έρπητας Ζωστήρας
Ασθενείς με «απορρύθμιση» του ανοσοποιητικού σ.





Έρπητας Ζωστήρας
Ηλικιωμένοι

Zerboni, Leigh & Sen, Nandini & Oliver, Stefan & Arvin, Ann. (2014). Nature reviews. Microbiology. 12. 10.1038/nrmicro3215.

Γιατί η σημερινή παρουσίαση…;

- Υψηλή επίπτωση σε ηλικιωμένους (40-50 ετών: 3/1000 → 60 έτη: 10/1000 ασθενο-έτη)
- Υψηλότερη επίπτωση σε ασθενείς με απορρύθμιση του ανοσοποιητικού συστήματος
- Υψηλότερη επίπτωση σε ασθενείς που λαμβάνουν ανοσοκατασταλτική θεραπεία

- Ενδείξεις αυξημένων ποσοστών αναζωπύρωσης ΕΖ σε ασθενείς με τα νεότερα tsDMARDs (JAKi)
- Δυσκολία στην αναγνώριση και προστασία (με προληπτικό εμβολιασμό) των ασθενών με ρευματικά νοσήματα
- Έλλειψη σε κατευθυντήριες οδηγίες σχετικά με την αντιμετώπιση των ασθενών που έχουν αυξημένο κίνδυνο ή εκδηλώνουν ΕΖ (όπως πχ σε HCV, HBV, LTB)

Yawn BP et al. Mayo Clin Proc 2011; 86:88–93
Kawai K et al. Infect Dis. 2016;63(2):221
Yun H. et al. Arthritis Rheumatol. 2016;68(9):2328
Winthrop, K. L. et al. Arthritis & Rheumatology, 69: 1960-1968 (2017)
Winthrop, K. L. et al. Arthritis & Rheumatology, 69: 1969-1977 (2017)

Υπάρχει πραγματική αύξηση του ΕΖ σε ασθενείς με ρευματικά νοσήματα;

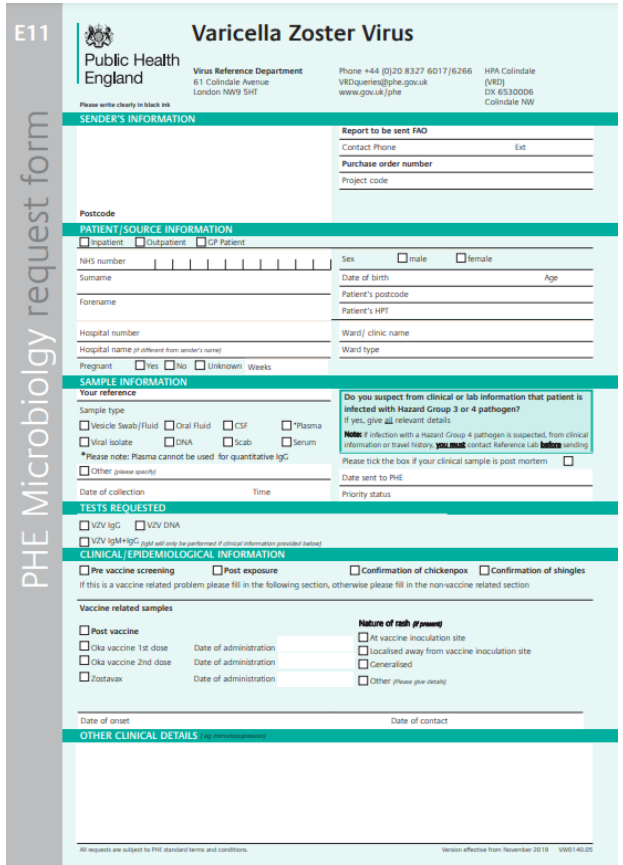
RHEUMATOLOGY

Rheumatology 2018;57:596–605
doi:10.1093/rheumatology/kex189
Advance Access publication 29 May 2017

Review

Managing varicella zoster virus contact and infection in patients on anti-rheumatic therapy

Matthew Cates[1], Matthew Donati[2], Sophie Gillet[3], Andrew Ustianowski[4] and James Galloway[5]



E11

PHE Microbiology request form

Public Health England

Varicella Zoster Virus

Virus Reference Department
61 Colindale Avenue
London NW9 5HT

Phone +44 (0)20 8327 6017/6266
VRDqueries@phe.gov.uk
www.gov.uk/phe

HPA Colindale (VRD)
DX 6530006
Colindale NW

Please write clearly in black ink

SENDER'S INFORMATION

Report to be sent FAO
Contact Phone Ext
Purchase order number
Project code
Postcode

PATIENT/SOURCE INFORMATION

Inpatient Outpatient GP Patient
NHS number
Sex male female
Surname
Date of birth Age
Forename
Patient's postcode
Patient's HPT
Hospital number
Hospital name (if different from sender's name)
Ward/ clinic name
Ward type
Pregnant Yes No Unknown Weeks

SAMPLE INFORMATION

Your reference
Sample type
Vesicle Swab/Fluid Oral Fluid CSF *Plasma
Viral isolate DNA Scab Serum
*Please note: Plasma cannot be used for quantitative IgG
Other (please specify)
Date of collection Time
Do you suspect from clinical or lab information that patient is infected with Hazard Group 3 or 4 pathogen?
If yes, give all relevant details
Note: If infection with a Hazard Group 4 pathogen is suspected, from clinical information or travel history, you must contact Reference Lab before sending
Please tick the box if your clinical sample is post mortem
Date sent to PHE
Priority status

TESTS REQUESTED

VZV IgG VZV DNA
VZV IgM+IgG (IgM will only be performed if clinical information provided below)

CLINICAL/EPIDEMIOLOGICAL INFORMATION

Pre vaccine screening Post exposure Confirmation of chickenpox Confirmation of shingles
If this is a vaccine related problem please fill in the following section, otherwise please fill in the non-vaccine related section
Vaccine related samples
Post vaccine
Oka vaccine 1st dose Date of administration
Oka vaccine 2nd dose Date of administration
Zostavax Date of administration
Nature of rash (if present)
At vaccine inoculation site
Localised away from vaccine inoculation site
Generalised
Other (Please give details)
Date of onset
Date of contact

OTHER CLINICAL DETAILS (eg immunosuppression)

All requests are subject to PHE standard terms and conditions.
Version effective from November 2019 VW01400.05

TABLE 1 Estimated rate of zoster patients with various risk factors, by age group

Key risk factors of interest	Rate of zoster/1000 person-years (99% CI)			
	<50 years	50–59 years	60–69 years	⩾70 years
General population (2010)	2.08 (1.74, 2.49)	4.37 (3.72, 5.12)	6.69 (5.76, 7.76)	8.84 (7.49, 10.43)
RA	3.51 (2.40, 5.13)	6.35 (3.46, 11.66)	9.96 (5.57, 17.77)	12.47 (6.94, 22.41)
SLE	6.32 (3.73, 10.74)	8.67 (3.2, 23.46)	8.20 (2.99, 22.45)	11.36 (4.22, 30.60)
IBD	3.59 (2.56, 5.04)	6.13 (3.55, 10.58)	8.67 (5.10, 14.74)	10.41 (6.10, 17.74)
Chronic obstructive pulmonary disease	2.31 (1.40, 3.84)	5.62 (2.44, 12.94)	9.19 (4.09, 20.62)	11.54 (5.08, 26.20)
Asthma	2.58 (2.03, 3.28)	5.20 (3.81, 7.11)	8.16 (6.04, 11.00)	10.44 (7.64, 14.25)
Chronic kidney disease	3.39 (2.38, 4.85)	5.51 (3.17, 9.59)	7.60 (4.52, 12.78)	9.70 (5.74, 16.37)
Depression	2.59 (2.03, 3.31)	4.89 (3.51, 6.80)	7.22 (5.19, 10.05)	9.71 (6.94, 13.58)
Diabetes	2.66 (1.99, 3.56)	4.84 (3.23, 7.27)	6.79 (4.62, 9.97)	8.55 (5.76, 12.70)
Type 1	3.14 (2.14, 4.67)	5.08 (2.32, 11.16)	6.55 (2.66, 16.12)	5.49 (1.75, 17.21)
Type 2	2.54 (1.84, 3.54)	4.77 (2.93, 7.78)	6.79 (4.25, 10.84)	8.54 (5.28, 13.79)

TABLE 2 Immunosuppressive risk of VZV infection with different medications, inferred from guidance from PHE

Low risk	Intermediate risk (PHE group A)	High risk (PHE group B)
Prednisolone, MTX or AZA at doses lower than in group A, SSZ, HCQ	Any of following in last 3 months: Prednisolone >40 mg/day for >1 week or >20 mg/day for >2 weeks MTX >25 mg/week AZA >3 mg/kg/day Mercaptopurine 1.5 mg/kg/day	Any of following in last 6 months: CYC Biologics Ciclosporin LEF

Withdrawn April 2022

Cates M. et al. Rheumatology 2018;57:596-605
Forbes HJ et al. BMJ 2014;348:g 2911.-598
https://www.gov.uk/government/ uploads/system/uploads/attachment_data/file/559469/ VZIG_ChickenPox_v4.pdf. 2016

Υπάρχει πραγματική αύξηση του ΕΖ σε ασθενείς με ρευματικά νοσήματα;

ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 9, September 2016, pp 2328–2337
DOI 10.1002/art.39670

Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases

Implications for Vaccination

Huifeng Yun,[1] Shuo Yang,[1] Lang Chen,[1] Fenglong Xie,[1] Kevin Winthrop,[2] John W. Baddley,[1] Kenneth G. Saag,[1] Jasvinder Singh,[1] and Jeffrey R. Curtis[1]

The herpes zoster (HZ) ***vaccine is recommended for adults age ≥ 60 years without weakened immune systems*** in the U.S. It is unclear how the risk of HZ varies according to age and disease conditions for younger patients with autoimmune or inflammatory (AI) diseases. ***We evaluated the age-stratified incidence of HZ associated with AI diseases compared to adults recommended for vaccination by the CDC***

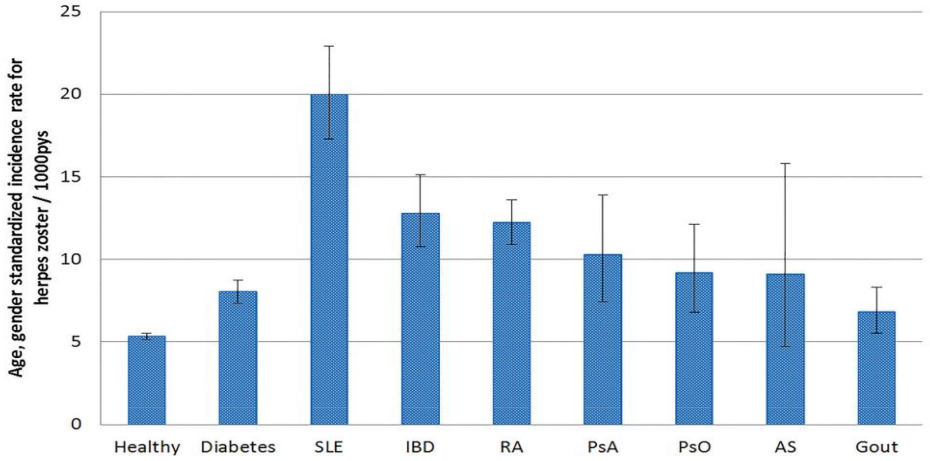


Figure 2. Age-standardized incidence rate for herpes zoster per 1000 pys, standardized to the U.S. 2010 census*
*among adults age >= 20
SLE = Systemic lupus erythematosus; IBD = Inflammatory bowel disease; RA = rheumatoid arthritis; PsO = psoriasis; PsA = Psoriatic arthritis; AS = Ankylosing spondylitis;

	Cohorts								
	Healthy*	Diabetes	SLE	IBD	RA	PsA	PsO	AS	Gout
	IR	IR	IR	IR	IR	IR	IR	IR	IR
Age group									
21–30	2.7	7.8	24.6	11.6	6.6	N/A	5.9	N/A	2.9
31–40	3.3	5.3	15.2	5.6	8.2	9.8	3.7	8.1	5.2
41–50	3.9	5.3	17.5	10.4	10.0	8.5	6.4	5.1	6.1
51–60	5.8	8.2	20	11.7	14.6	13.2	9.7	8.3	6.9
61–70	8.5 (referent)	11.0	22.7	19.0	17.1	15.9	13.3	14.3	9.5
71–85+	10.6	13.0	20.9	23.8	21.3	19.4	21.2	26.3	13.3

*Individuals without autoimmune, inflammatory conditions or diabetes

IR: Incidence per 1000 person years

Conclusions—SLE, IBD and RA are associated with higher risks of HZ compared to older adults recommended for vaccination, suggesting that individuals with these conditions as young as age 40 could potentially benefit from vaccination.

Yun H. et al. Arthritis Rheumatol. 2016 September ; 68(9): 2328–2337

Υπάρχει αύξηση του ΕΖ σε ασθενείς με ρευματικά νοσήματα λόγω ανοσοκαταστολής;

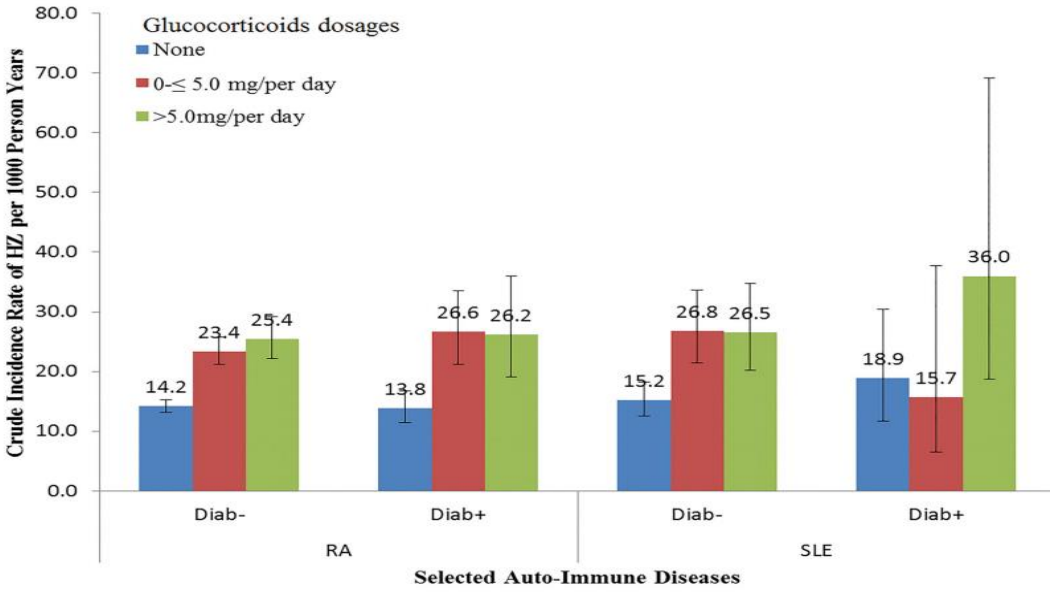


Figure 3.
Incidence rate based on different combination of diabetes and glucocorticoids dosages, using RA and SLE as examples

Table 5. Association between medication use and herpes zoster among patients with rheumatoid arthritis in the UK General Practice Research Database*

Medication†	Cases (n = 1,719)	Controls (n = 12,033)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)‡
No DMARDs or oral corticosteroids	1,084 (63.1)	8,869 (73.7)	Reference	Reference
Traditional DMARDs only	273 (15.9)	1,633 (13.6)	1.36 (1.81–1.57)	1.27 (1.10–1.48)
Oral corticosteroids only	240 (14.0)	1,061 (8.8)	1.84 (1.58–2.15)	1.46 (1.24–1.70)
Traditional DMARDs and oral corticosteroids	122 (7.1)	470 (3.9)	2.13 (1.73–2.63)	1.82 (1.46–2.26)

* Values are the number (percentage) unless otherwise indicated. OR = odds ratio; 95% CI = 95% confidence interval; DMARDs = disease-modifying antirheumatic drugs.
† The categories related to current DMARD/oral corticosteroid exposure are mutually exclusive.
‡ Adjusted for age, sex, current cyclooxygenase 2 inhibitor and nonsteroidal antiinflammatory drug use, comorbidities (diabetes, chronic lung disease, and cancer), history of an orthopedic procedure, number of visits to a health care provider between cohort entry and the index date, and whether or not the patient saw a rheumatologist during followup.

Αναδρομικές μελέτες σε ασθενείς που καταγράφηκαν μέσα από τα συστήματα υγείας (ΗΠΑ/ΗΒ)

Ανεξάρτητα από τους παράγοντες κινδύνου για ΕΖ στο γενικό πληθυσμό (πχ ηλικία, συνοσηρότητες)

Αύξηση του κινδύνου για εμφάνιση έρπητα ζωστήρα παρατηρείται:

- Λόγω της «φύσης» του νοσήματος
- Ανεξάρτητα από συνοσηρότητα
- Λόγω της θεραπευτικής παρέμβασης (ανοσοκαταστολή)
- Ο κίνδυνος είναι υψηλότερος όσο ισχυρότερη ανοσοκαταστολή (πχ συνδυασμός κορτικοστεροειδών και DMARDs)

Yun H. et al. Arthritis Rheumatol. 2016 September ; 68(9): 2328–2337

Smitten AL et al. Arthritis Rheum. 2007 Dec 15;57(8):1431-8.

Ρευματοειδής Αρθρίτιδα

Arthritis Care & Research
Vol. 67, No. 12, December 2015, pp 1671–1678
DOI 10.1002/acr.22628

ORIGINAL ARTICLE

Corrona registry (ΗΠΑ)

Herpes Zoster Reactivation in Patients With Rheumatoid Arthritis: Analysis of Disease Characteristics and Disease-Modifying Antirheumatic Drugs

DIMITRIOS A. PAPPAS,[1] MICHELE M. HOOPER,[2] JOEL M. KREMER,[3] GEORGE REED,[4] YING SHAN,[5] DEBORAH WENKERT,[2] JEFFREY D. GREENBERG,[6] AND JEFFREY R. CURTIS[7]

- 28,852 ασθενείς
- 95,287 ασθενο-έτη
- Γενική επίπτωση ΕΖ: 7.7 ανά 1,000 ασθενο-έτη
- Ανάλυση ως ***Μάρτιο 2013***

❑ **Παράγοντες κινδύνου**

- ➢ **Ηλικία**
- ➢ ***Κορτικοστεροειδή > 7,5mg/ημέρα***

➢ **Όχι διαφορές σε ενεργότητα νόσου, status οροθετικότητας, αριθμό προηγούμενων DMARDs,συνοσηρότητες**

Table 2. Bivariate and Cox regression and multivariable-adjusted estimated hazard ratios (HRs) with HZ*

Characteristics	Bivariate age-adjusted HR (95% CI)	Multivariate age-adjusted HR (95% CI)
Age, years (for every 5 years)	1.13 (1.08–1.17)	1.14 (1.09–1.19)
Female	1.21 (0.95–1.53)	
mHAQ	1.23 (1.01–1.51)	1.11 (0.87–1.43)
Duration RA	1.00 (0.99–1.01)	
Prednisone dose (category):		
No use	1 (referent)	1 (referent)
1–7.4 mg	1.13 (0.88–1.46)	1.12 (0.87–1.46)
≥7.5 mg	1.86 (1.28–2.72)	1.78 (1.20–2.63)
CDAI	1.01 (1.00–1.02)	
CDAI category:		
Remission (≤2.8)	1 (referent)	1 (referent)
Low (>2.8–10)	1.21 (0.94–1.56)	1.17 (0.89–1.55)
Moderate (>10–22)	1.23 (0.93–1.62)	1.11 (0.81–1.52)
High (>22)	1.38 (1.004–1.91)	1.15 (0.78–1.70)
History of diabetes mellitus	1.26 (0.91–1.74)	1.27 (0.90–1.80)
History of cancer	1.04 (0.76–1.42)	1.03 (0.74–1.44)
History of stroke	1.39 (0.84–2.31)	
History of CVD	1.10 (0.77–1.58)	1.07 (0.73–1.56)
No. prior biologic agents		
0	1 (referent)	1 (referent)
1	1.21 (0.94–1.55)	1.15 (0.77–1.72)
≥2	1.44 (1.10–1.89)	1.40 (0.91–2.16)
Current medications		
TNF inhibitors		1 (referent)
Non-TNF inhibitor biologic agent		0.62 (0.41–0.93)
Conventional synthetic DMARDs		0.94 (0.65–1.35)

* Each factor (except age) is age adjusted. HZ = herpes zoster; 95% CI = 95% confidence interval; mHAQ = modified Health Assessment Questionnaire; RA = rheumatoid arthritis; CDAI = Clinical Disease Activity Index; CVD = cardiovascular disease; TNF = tumor necrosis factor; DMARD = disease-modifying antirheumatic drug.

Pappas D.. et al Arthritis Care & Research Vol. 67, No. 12, December 2015, pp 1671–167

Ρευματοειδής Αρθρίτιδα

Arthritis Care & Research
Vol. 67, No. 12, December 2015, pp 1671–1678
DOI 10.1002/acr.22628

ORIGINAL ARTICLE

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- 28,852 ασθενείς
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- Ανάλυση ως ***Μάρτιο 2013***

- ❖ Καμία διαφορά και στον κίνδυνο μεταξύ των θεραπευτικών κατηγοριών
- ❖ Αριθμητικά αυξημένος κίνδυνος στα csDMARDs

Table 4. HZ events per patient-year of followup after propensity score trimming and stratification*

Drug	Patient-years	Events, no.	Incidence rate per 1,000 patient-years	95% CI
TNF inhibitors	7,626.2	53	6.9	5.3–9.1
Non–TNF inhibitor biologic agents	3,667.2	25	6.8	4.6–10.1
Conventional synthetic DMARDs	2,100.4	22	10.5	6.9–15.9
Total	13,393.8	100	7.5	6.1–9.1

* HZ = herpes zoster; 95% CI = 95% confidence interval; TNF = tumor necrosis factor; DMARDs = disease-modifying antirheumatic drugs.

Table 5. HZ hazard ratios (HRs): unadjusted and adjusted Cox regression models*

Treatment	HR†	95% CI	*P*
Unadjusted Cox regression model			
TNF inhibitors (reference)	1		
Non-TNF inhibitor biologic agents	0.982	0.609–1.585	0.942
Conventional synthetic DMARD	1.552	0.942–2.557	0.084
Adjusted Cox regression model‡			
TNF inhibitors (reference)	1		
Non-TNF inhibitor biologic agents	0.834	0.509–1.367	0.472
Conventional synthetic DMARD	1.359	0.819–2.253	0.235

* HZ = herpes zoster; 95% CI = 95% confidence interval; TNF = tumor necrosis factor; DMARD = disease-modifying antirheumatic drug.
† Stratified by propensity score quintiles using multinomial logistic regression; covariates are age, sex, prednisone use, modified Health Assessment Questionnaire, Clinical Disease Activity Index, history of cancer, and history of diabetes mellitus.
‡ Adjusted Cox regression model, for stratified data, adjusted with propensity score quintile.

Pappas D.. et al Arthritis Care & Research Vol. 67, No. 12, December 2015, pp 1671–167

Ρευματοειδής Αρθρίτιδα

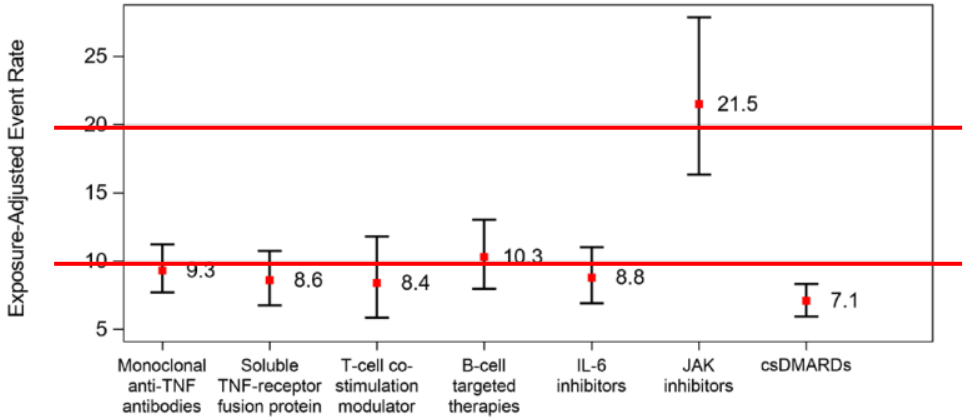
Rheumatoid arthritis

EPIDEMIOLOGICAL SCIENCE

RABBIT registry (Γερμανία)

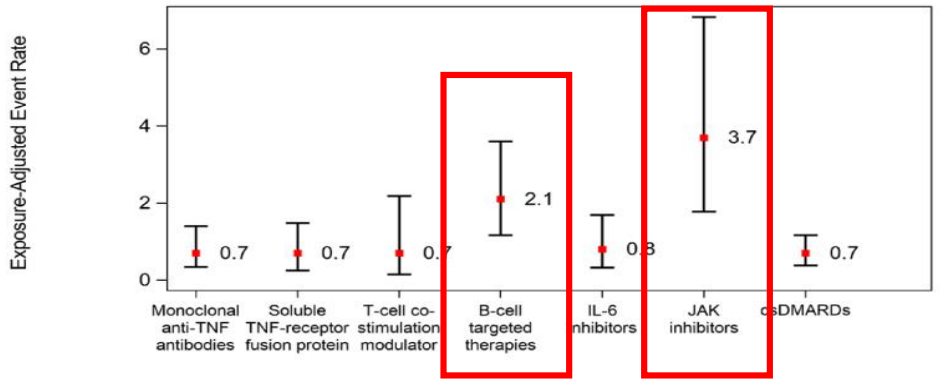
Risk of herpes zoster (shingles) in patients with rheumatoid arthritis under biologic, targeted synthetic and conventional synthetic DMARD treatment: data from the German RABBIT register

Imke Redeker [1], Katinka Albrecht [1], Joern Kekow [2], Gerd Rüdiger Burmester [3], Juergen Braun [4], Martin Schäfer [1], Angela Zink [1], Anja Strangfeld [1]



Patient-years	12207	8850	4027.6	6522.9	8543.9	2691.5	20114
No. events	114	76	34	67	75	58	142
95% CI	7.7-11.2	6.8-10.8	5.9-11.8	8.0-13.0	6.9-11.0	16.4-27.9	6.0-8.3

- 13.991 ασθενείς
- 62.958 ασθενο-έτη
- EAER EZ: 8.9 ανά 1000 ασθενο-έτη
- Ανάλυση ως ***2007 - 2020***



Patient-years	12207	8850	4027.6	6522.9	8543.9	2691.5	20114
No. serious events	9	6	3	14	7	10	14
95% CI	0.3-1.4	0.3-1.5	0.2-2.2	1.2-3.6	0.3-1.7	1.8-6.8	0.4-1.2

- Καμία διαφορά και στον κίνδυνο μεταξύ των **bDMARDs**
- Αριθμητικά χαμηλότερος κίνδυνος στα **csDMARDs**
- Αυξημένος κίνδυνος με **JAKi** (x 3.6)
- Αυξημένος κίνδυνος με JAKi **ανεξάρτητος με ΚΣ**
- Αυξημένος κίνδυνος για σοβαρά επεισόδια ΕΖ με **Bcell-depletion therapy και JAKi**

Redeker I, Albrecht K, Kekow J, et al. Ann Rheum Dis 2022;81:41–47

Ρευματοειδής Αρθρίτιδα

Treatments

RMD Open
Rheumatic & Musculoskeletal Diseases

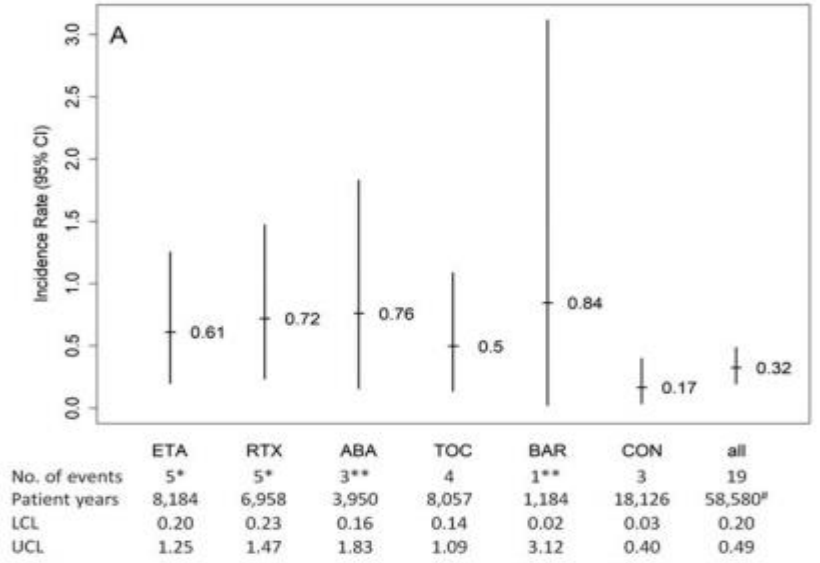
Short report

Incidence of facial nerve palsies stratified by DMARD treatment in patients with rheumatoid arthritis: data from the RABBIT register

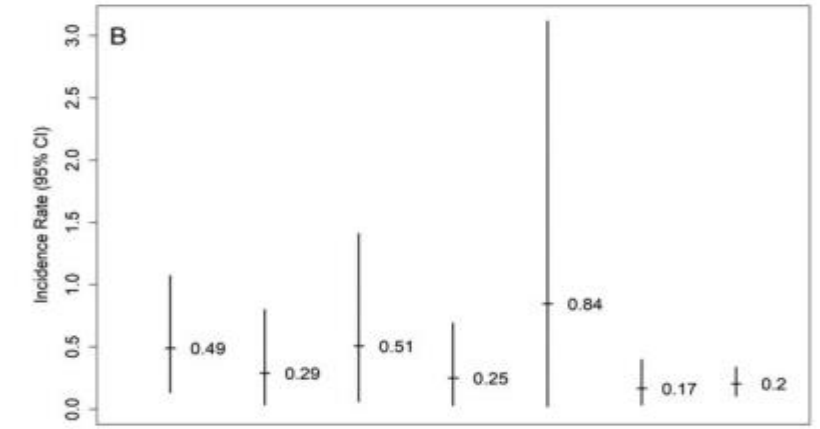
RABBIT registry (Γερμανία)

Yvette Meissner,[1] Martin Schäfer,[1] Matthias Schneider,[2] Elke Wilden,[3] Silke Zinke,[4] Angela Zink,[1] Anja Strangfeld[1]

- 14.185 ασθενείς
- Πάρεση: 10 – Παράλυση: 12 (Προσωπικού νεύρου)
- Ανάλυση ως ***2007 - 2020***



	ETA	RTX	ABA	TOC	BAR	CON	all
No. of events	5*	5*	3**	4	1**	3	19
Patient years	8,184	6,958	3,950	8,057	1,184	18,126	58,580#
LCL	0.20	0.23	0.16	0.14	0.02	0.03	0.20
UCL	1.25	1.47	1.83	1.09	3.12	0.40	0.49



	ETA	RTX	ABA	TOC	BAR	CON	all
No. of events	4*	2*	2**	2	1**	3	12
Patient years	8,184	6,958	3,950	8,057	1,184	18,126	58,580#
LCL	0.13	0.03	0.06	0.03	0.02	0.03	0.11
UCL	1.07	0.80	1.41	0.69	3.12	0.40	0.34

❖ ***Ιδιος κίνδυνος με γενικό πληθυσμό:***

- Συχνότητα ΠΠΝ bDMARDs > csDMARDs
- Καμία συσχέτιση με συνοσηρότητες ή συγκεκριμένη θεραπευτική κατηγορία

Meissner Y, Schäfer M, Schneider M, et al. RMD Open 2020;6:e001403

Ρευματοειδής Αρθρίτιδα

Rheumatoid arthritis

EPIDEMIOLOGICAL SCIENCE

RABBIT registry (Γερμανία)

Risk of herpes zoster (shingles) in patients with rheumatoid arthritis under biologic, targeted synthetic and conventional synthetic DMARD treatment: data from the German RABBIT register

Imke Redeker ,[1] Katinka Albrecht ,[1] Joern Kekow,[2] Gerd Rüdiger Burmester ,[3] Juergen Braun ,[4] Martin Schäfer,[1] Angela Zink,[1] Anja Strangfeld [1]

- 13.991 ασθενείς
- 62.958 ασθενο-έτη
- EAER EZ: 8.9 ανά 1000 ασθενο-έτη
- Ανάλυση ως ***2007 - 2020***

❖ ***Παράγοντες κινδύνου σε αλλαγή θεραπείας:***

- Γυναικείο φύλο, ηλικία
- Κορτικοστεροειδή > 10mg
- Μονοκλωνικό Ab TNFi
- B-depletion
- JAKi

Table 4 Risk of herpes zoster for patients who were either enrolled with bDMARD/tsDMARD treatment and had interruption(s) during follow-up in the course of which they received csDMARDs alone or who were enrolled with csDMARD treatment and started bDMARD/tsDMARD treatment during follow-up

	Andersen-Gill model	
Characteristics	**Adjusted HR (95% CI)**	**P value**
Female sex	1.64 (1.20 to 2.24)	**0.0018**
Age per 10 years	1.31 (1.19 to 1.44)	**<0.0001**
Glucocorticoids, 5–10 vs 0 mg/day	1.24 (0.98 to 1.57)	0.0763
Glucocorticoids, >10 vs 0 mg/day	3.45 (2.14 to 5.55)	**<0.0001**
csDMARD treatment	*Reference*	
Monoclonal anti-TNF antibodies	1.87 (1.31 to 2.69)	**0.0006**
Soluble TNF receptor fusion protein	1.35 (0.87 to 2.10)	0.1819
T cell costimulation modulator	1.60 (0.98 to 2.59)	0.0581
B cell targeted therapy	1.71 (1.22 to 2.39)	**0.0019**
IL-6 inhibitors	1.48 (0.97 to 2.25)	0.0673
JAK inhibitors	3.51 (2.24 to 5.52)	**<0.0001**

P values <0.05 are shown in bold.
bDMARDs, biologic DMARDs; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs; IL-6, interleukin 6; JAK, Janus kinase; TNF, tumour necrosis factor; tsDMARDs, targeted synthetic DMARDs.

Redeker I, Albrecht K, Kekow J, et al. Ann Rheum Dis 2022;81:41–47

Ρευματοειδής Αρθρίτιδα

Herpes Zoster and Tofacitinib

Clinical Outcomes and the Risk of Concomitant Therapy

Kevin L. Winthrop,[1] Jeffrey R. Curtis,[2] Stephen Lindsey,[3] Yoshiya Tanaka,[4] Kunihiro Yamaoka,[5] Hernan Valdez,[6] Tomohiro Hirose,[7] Chudy I. Nduaka,[8] Lisy Wang,[9] Alan M. Mendelsohn,[8] Haiyun Fan,[8] Connie Chen,[6] and Eustratios Bananis[8]

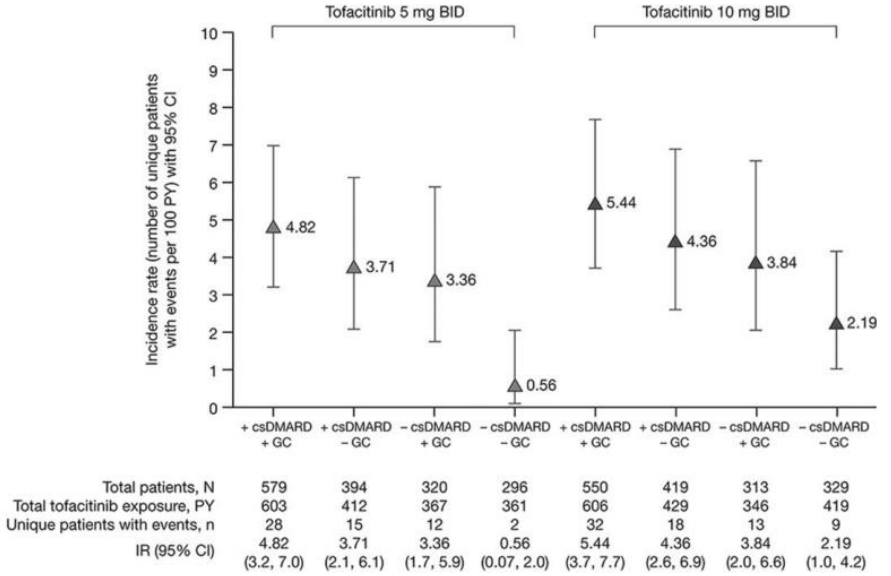
Μελέτες tofacitinib φάσης III

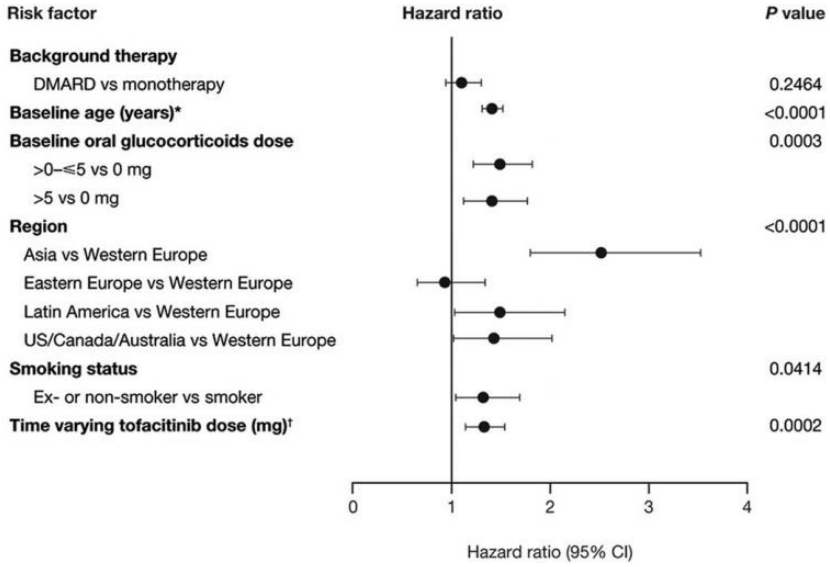
- 6,192 ασθενείς
- 16,839 ασθενο-έτη
- IR: 4.0, 95% CI 3.7–4.4
- 93% non serious – 94% 1 δερμοτόμιο
- Γεωγραφική κατανομή

❖ ***Παράγοντες κινδύνου:***

- Συγχορήγηση ΚΣ - όχι csDMARDs
- Κορτικοστεροειδή > 10mg
- Ασιατική καταγωγή

RABBIT registry (Γερμανία)

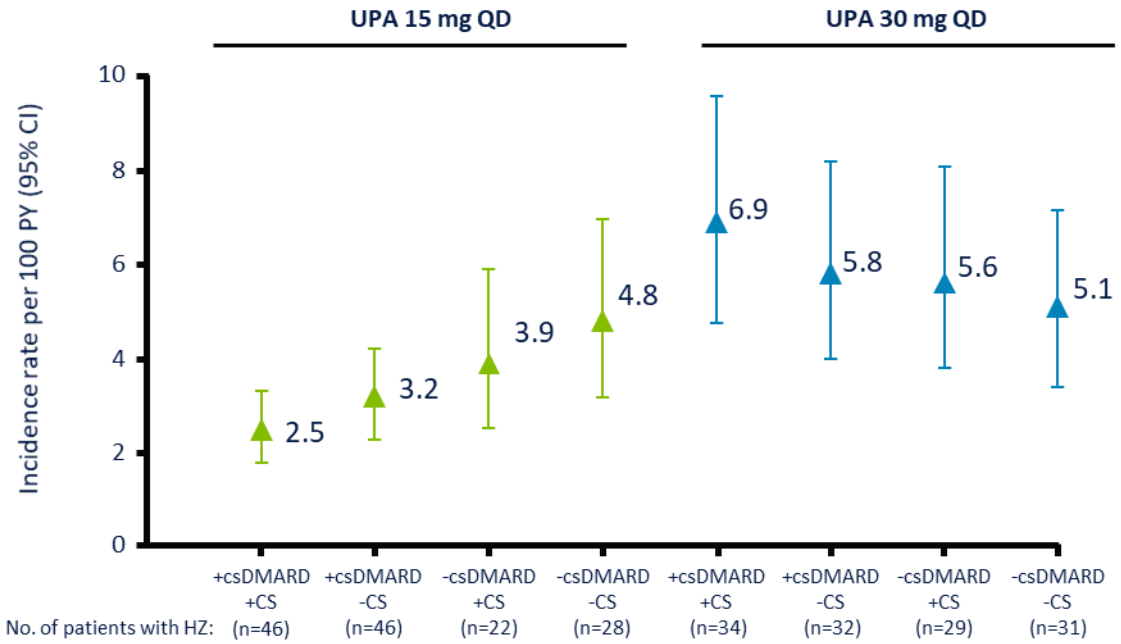




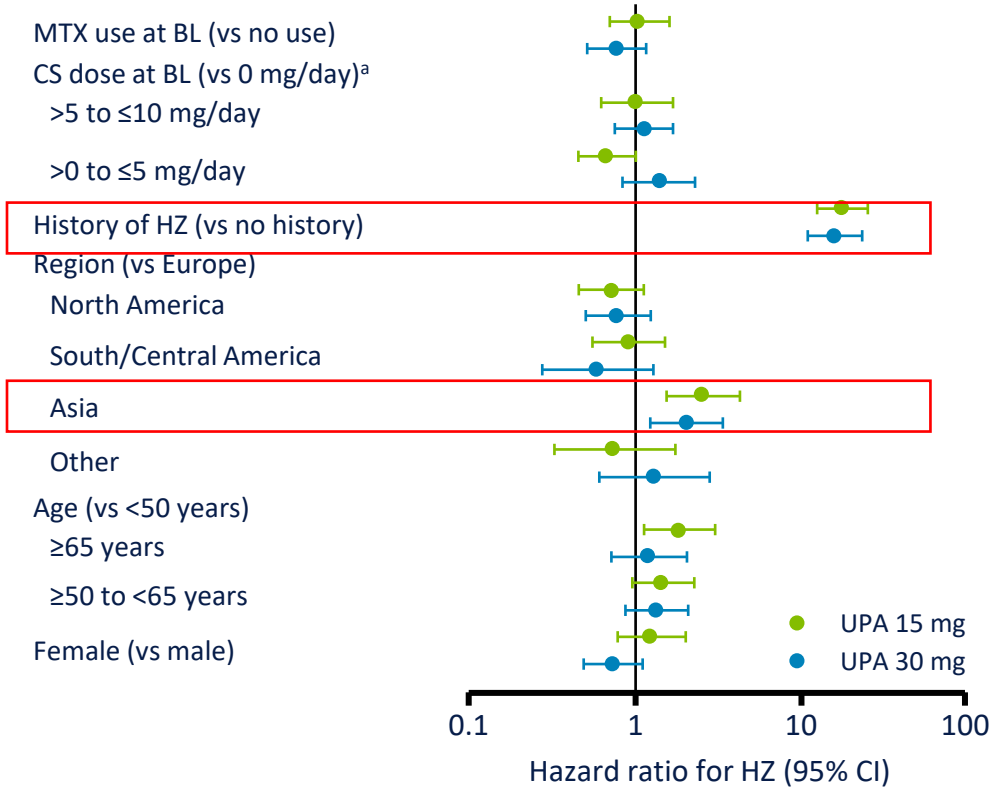
Winthrop KL. et al. Arthritis & Rheumatology Vol. 69, No. 10, October 2017, pp 1960–1968

Ρευματοειδής Αρθρίτιδα

Επίπτωση ΕΖ ανά csDMARD και χορήγηση ΚΣ σε ασθενείς με ΡΑ υπό UPA



Παράγοντες κινδύνου για ΕΖ (πολυπαραγοντική ανάλυση)



- Η συγχορήγηση ΚΣ ή csDMARD δεν αύξησε τον κίνδυνο
- Η προηγούμενη λοίμωξη είναι σημαντικός παράγοντας κινδύνου;
- Η ασιατική καταγωγή αλλάζει τα δεδομένα;

CI, confidence interval; CS, corticosteroid; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HZ, herpes zoster; PY, patient-year; QD, once daily; UPA, upadacitinib

aPrednisone or equivalent dose

Winthrop K, et al. EULAR 2020: THU0218

Ψωριασική Αρθρίτιδα και ΕΖ

Clalit Health Services (CHS) – Ισραήλ

- 3128 ασθενείς
- 20.096 ασθενο-έτη
- 2002 – 2012 (Αναδρομική μελέτη)
- (Cr)IR: 9.06 (95% CI)

EXTENDED REPORT

Psoriatic arthritis treatment and the risk of herpes zoster

D Zisman,[1,2] H Bitterman,[2,3] G Shalom,[3] I Feldhamer,[3] D Comanesther,[3] E Batat,[3] S Greenberg-Dotan,[3] S Cohen,[1] A D Cohen[3,4]

✓ Παράγοντες κινδύνου:
- ➢ Ηλικία
- ➢ Κορτικοστεροειδή
- ➢ Συγχορήγηση TNFi - csDMARD

❖ Καμία διαφορά στον κίνδυνο μεταξύ των **bDMARDs – csDMARDs** σε μονοθεραπεία

Table 3 Time to herpes zoster event according to the Cox proportional hazard model

Model	Characteristics	B	SE	HR	CI (95%)	p Value
Model 1	Age	0.01	0.006	1.01	1.00 to 1.02	0.048
	Sex—female	0.25	0.156	1.29	0.95 to 1.75	0.11
	Charlson Comorbidity Index score	0.04	0.058	1.04	0.93 to 1.17	0.46
	Steroid exposure	0.08	0.023	1.08	1.04 to 1.13	<0.001
	Treatment previous to 2002 with c-DMARDs	−0.06	0.172	0.94	0.67 to 1.32	0.73
	Group A-(no DMARDs)	Ref.		1.00		
	Group B-(c-DMARDs)	0.10	0.194	1.11	0.76 to 1.62	0.60
	Group C-(anti-TNF-α)	0.25	0.318	1.28	0.69 to 2.4	0.43
	Group D-(anti-TNF-α + c-DMARDs)	0.86	0.296	2.37	1.32 to 4.22	0.004
Model 2	Age	0.01	0.006	1.01	1.01 to 1.02	0.049
	Sex—female	0.25	0.156	1.29	0.95 to 1.75	0.10
	Charlson Comorbidity Index score	0.04	0.058	1.04	0.93 to 1.17	0.47
	Steroid exposure	0.08	0.023	1.08	1.04 to 1.13	<0.001
	Treatment previous to 2002 with c-DMARDs	−0.06	0.172	0.94	0.67 to 1.32	0.71
	Group A-(no DMARDs)	Ref.		1.00		
	Group B-(c-DMARDs)	0.10	0.194	1.11	0.76 to 1.62	0.59
	Group E-(MAB-anti-TNF-α)	0.16	0.424	1.18	0.51 to 2.70	0.70
	Group F-(MAB-anti-TNF-α + c-DMARDs)	0.62	0.356	1.86	0.93 to 3.75	0.08
	Group G-(etanercept)	0.34	0.396	1.41	0.65 to 3.06	0.39
	Group H-(etanercept + c-DMARDs)	1.28	0.391	3.60	1.67 to 7.75	0.001

*Steroid exposure was defined as the number of prescriptions of steroid-containing preparations filled at the pharmacy during treatment period.
DMARD, disease-modifying anti-rheumatic drug.

Zisman D, Bitterman H, Shalom G, et al Ann Rheum Dis. 2016;75(1):131-135.

Ψωριασική Αρθρίτιδα και ΕΖ

US Medicare dataset 2006-2011– ΗΠΑ

ABSTRACT NUMBER: 1589

Risk of Opportunistic Infection and Herpes Zoster Infection in a Psoriasis/Psoriatic Arthritis Cohort

Kevin L. Winthrop[1], Lang Chen[2], John Baddley[2], Allison Taylor[3], Benjamin Chan[4], Huifeng Yun[5], Sarah Siegel[6] and Jeffrey R. Curtis[7], [1]Dept of Infectious Disease, Oregon Health & Science University, Portland, OR, [2]Medicine, University of Alabama at Birmingham, Birmingham, AL, [3]Clinical Immunology/Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [4]Oregon Health and Science University, Portland, OR, [5]Epidemiology, University of Alabama at Birmingham School of Public Health, Birmingham, AL, [6]Oregon Health & Science University, Portland, OR, [7]The University of Alabama at Birmingham, Birmingham, AL

Meeting: 2014 ACR/ARHP Annual Meeting

- 10,261 PsA - 31,052 PsO
- ΨΑ: 16.1 (95% CI: 12.8-20.0) ανά 1,000 ασθενο-έτη
- 2006 – 2011 (Αναδρομική μελέτη)

❖ Καμία διαφορά στον κίνδυνο μεταξύ των **bDMARDs – csDMARDs**

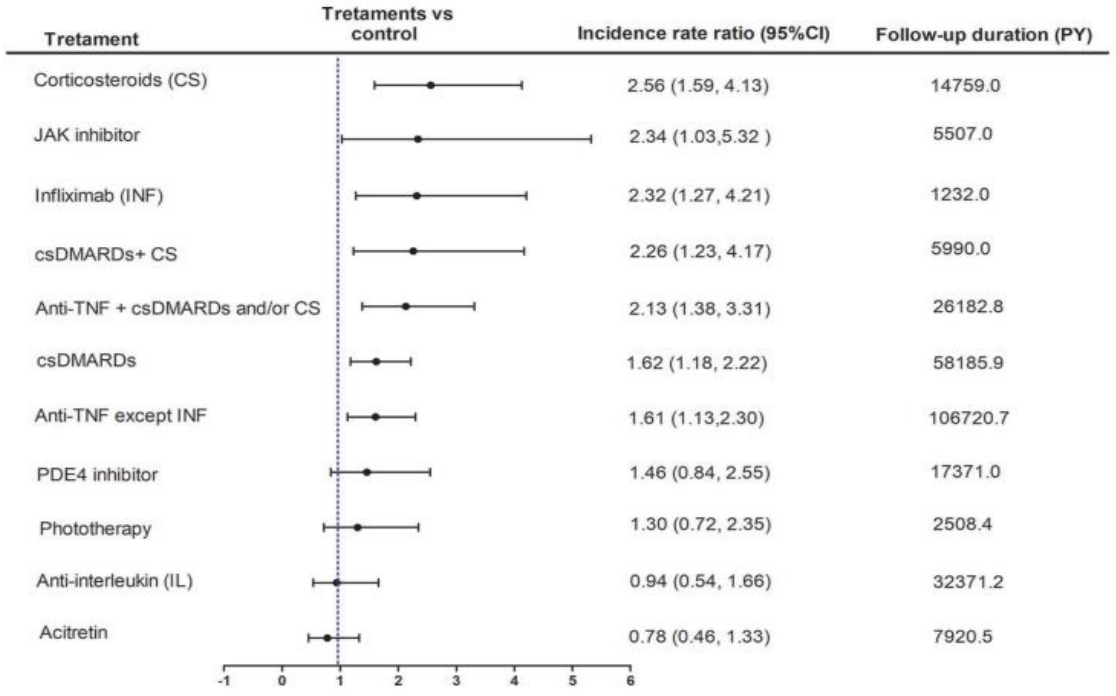
✓ ***Περισσότερο αυξημένος κίνδυνος με :***

- ***Κορτικοστεροειδή***
- ***JAKi***
- ***Infliximab***

Network meta-analysis RCTs

Comparative risk of herpes zoster in patients with psoriatic disease on systemic treatments: a systematic review and network meta-analysis

Hsien-Yi Chiu*, Yi-Teng Hung*, Shi-Wei Huang and Yu-Huei Huang



Winthrop K. et al. Arthr & Rheum 2020 Suppl.
Chiu HY et al. Ther Adv Chronic Dis 2022, Vol. 13: 1–11

Αγκυλοποιητική Σπονδυλίτιδα και ΕΖ

MODERN RHEUMATOLOGY, 2017
https://doi.org/10.1080/14397595.2017.1325034

MODERN RHEUMATOLOGY | Taylor & Francis

ORIGINAL ARTICLE

The risk of herpes zoster in patients with ankylosing spondylitis: Analysis of the Korean National Health Insurance Service – Sample cohort database

Doo-Ho Lim[a], Ye-Jee Kim[b], Seon Ok Kim[b], Seokchan Hong[c], Chang-Keun Lee[c], Bin Yoo[c] and Yong-Gil Kim[c]

- Ασιατικός πληθυσμός
- IR: 11.0 ανά 1000 ασθενο-έτη
- Αυξημένος κίνδυνος με ***χρήση TNFi***
- Αυξημένος κίνδυνος με ***χρήση ΚΣ*** (και συγχορήγηση) (pos)
- Αυξημένος κίνδυνος σε ***Switch θεραπείας***
- ***Αναδρομικές μελέτες (μόνο csDMARDs και TNFi)***

Table 2. Incidence rate of herpes zoster in patients with AS according to medication use.

Medication use	Number of herpes zoster	Person-years of medication use	Incidence rate (per 1000 person-years) (95% CI)
Total	54	4931.41	11.0 (8.2–14.3)
DMARD nonusers	32	3524.4	9.1 (6.2–12.8)
cDMARD users	14	839.2	16.7 (9.1–28.0)
TNFα inhibitor users	8	567.8	14.1 (6.1–27.8)

CI: confidence interval.

Table 3. Hazard ratios of herpes zoster in patients with AS according to medication use.

Medication use	Crude hazard ratio (95% CI)	Adjusted hazard ratio† (95% CI)
DMARD non-users	1.00 (reference)	1.00 (reference)
cDMARD users	3.11 (1.47–6.58)	3.70 (9.1–28.0)
TNFα inhibitor users	2.60 (1.09–6.19)	3.52 (6.1–27.8)

[b]Adjusted for sex, age, and baseline corticosteroid use.
CI: confidence interval.

Received: 11 December 2018 | Revised: 19 May 2019 | Accepted: 13 June 2019
DOI: 10.1111/1756-185X.13650

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases | WILEY

The risk of herpes zoster among patients with ankylosing spondylitis: A population-based cohort study in Taiwan

Shuya Wang[1] | James Cheng-Chung Wei[2,3,4,5] | Jing-Yang Huang[3,6] | Wuu-Tsun Perng[7] | Zhiyi Zhang[1]

- Ασιατικός πληθυσμός
- IR: 5.54 controls ανά ασθενο-έτη vs 6.52 σε ΑΣ
- Μονο MTX και SSZ

❖ ***Η θεραπευτική παρέμβαση παίζει τον κύριο ρόλο στην εμφάνιση ΕΖ***

	Control N = 11 276	AS patients N = 2819	*P* value
Follow-up person months	816 752	204 188	
Event of HZ	377	111	
Incidence rate[a] (95% CI)	5.54 (5.01-6.13)	6.52 (5.42-7.86)	
Model 1: Crude HR (95% CI)	Reference	1.178 (0.953-1.455)	0.1298
Model 2: aHR (95% CI)[b]	Reference	1.180 (0.955-1.458)	0.1260
Model 3: aHR (95% CI)[c]	Reference	1.103 (0.888-1.369)	0.3752
Model 4: aHR (95% CI)[d]	Reference	1.071 (0.836-1.372)	0.5857

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; AS, ankylosing spondylitis; HZ, herpes zoster.
[a]Per 1000 person-years.
[b]Model 2: adjusted demographic variables at baseline including age, sex and urbanization.
[c]Model 3: adjusted demographics, length of hospital stay and comorbidities at baseline.
[d]Model 4: adjusted demographics, length of hospital stay, comorbidities and medication at baseline.

Lim et al. Modern Rheumatology 2017
Wang, S, Wei, JC-C, Huang, J-Y, Perng, W-T, Zhang, Z. Int J Rheum Dis. 2020; 23: 181– 188.

ΣΕΛ και ΕΖ

ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 9, September 2016, pp 2328–2337
DOI 10.1002/art.39670

Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases

Implications for Vaccination

Huifeng Yun,[1] Shuo Yang,[1] Lang Chen,[1] Fenglong Xie,[1] Kevin Winthrop,[2] John W. Baddley,[1] Kenneth G. Saag,[1] Jasvinder Singh,[1] and Jeffrey R. Curtis[1]

The herpes zoster (HZ) ***vaccine is recommended for adults age ≥ 60 years without weakened immune systems*** in the U.S. It is unclear how the risk of HZ varies according to age and disease conditions for younger patients with autoimmune or inflammatory (AI) diseases. ***We evaluated the age-stratified incidence of HZ associated with AI diseases compared to adults recommended for vaccination by the CDC***

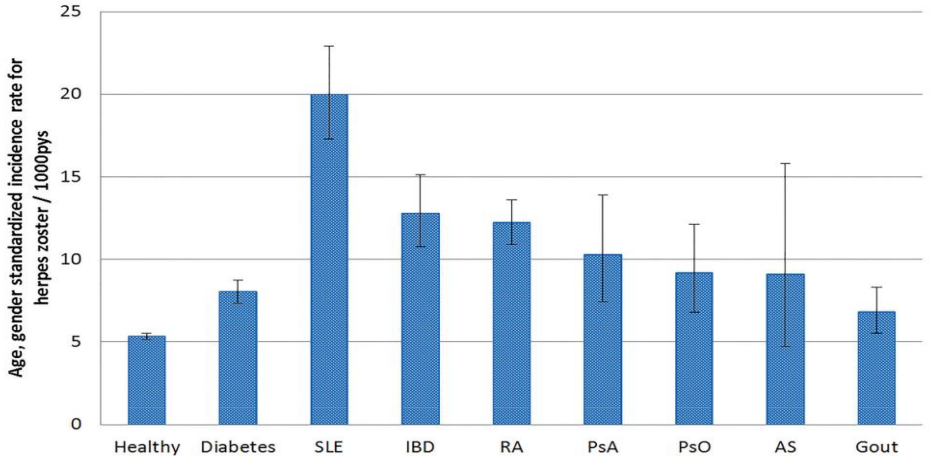


Figure 2. Age-standardized incidence rate for herpes zoster per 1000 pys, standardized to the U.S. 2010 census*
*among adults age >= 20
SLE = Systemic lupus erythematosus; IBD = Inflammatory bowel disease; RA = rheumatoid arthritis; PsO = psoriasis; PsA = Psoriatic arthritis; AS = Ankylosing spondylitis;

	Cohorts								
	Healthy*	Diabetes	SLE	IBD	RA	PsA	PsO	AS	Gout
	IR	IR	IR	IR	IR	IR	IR	IR	IR
Age group									
21–30	2.7	7.8	24.6	11.6	6.6	N/A	5.9	N/A	2.9
31–40	3.3	5.3	15.2	5.6	8.2	9.8	3.7	8.1	5.2
41–50	3.9	5.3	17.5	10.4	10.0	8.5	6.4	5.1	6.1
51–60	5.8	8.2	20	11.7	14.6	13.2	9.7	8.3	6.9
61–70	8.5 (referent)	11.0	22.7	19.0	17.1	15.9	13.3	14.3	9.5
71–85+	10.6	13.0	20.9	23.8	21.3	19.4	21.2	26.3	13.3

*Individuals without autoimmune, inflammatory conditions or diabetes

IR: Incidence per 1000 person years

ΣΕΛ: Αυξημένος κίνδυνος για έρπητα ζωστήρα από την εμφάνιση (20 ετών) !!

Yun H. et al. Arthritis Rheumatol. 2016 September ; 68(9): 2328–2337

ΣΕΛ και κίνδυνος ΕΖ

ABSTRACT NUMBER: 605

Increased Incidence of Herpes Zoster Among Patients with Systemic Lupus Erythematosus

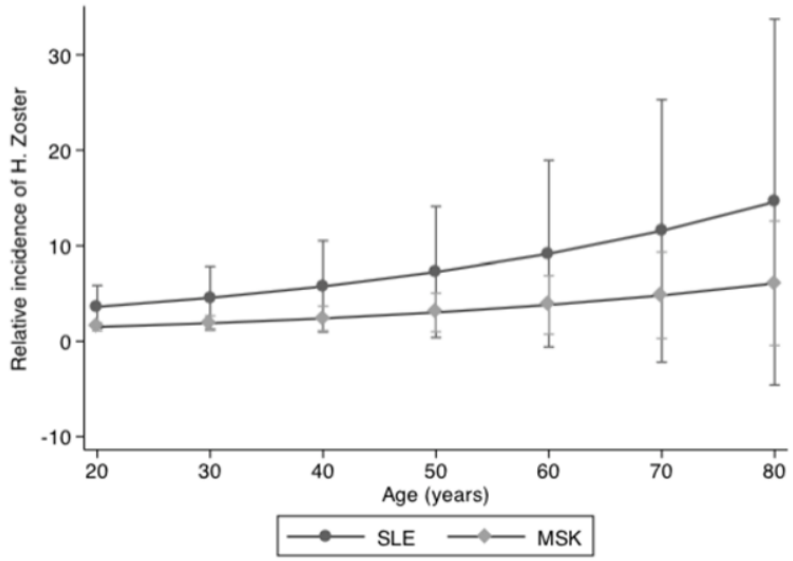
Eliza F. Chakarvarty[1], Kaleb Michaud[2], Robert S. Katz[3] and Frederick Wolfe[4], [1]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, CA, [2]Rheumatology, National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE, [3]Rush University Medical Center, Chicago, IL, [4]National Data Bank for Rheumatic Diseases, Wichita, KS

Meeting: 2012 ACR/ARHP Annual Meeting

National Data Bank for Rheumatic Diseases (NDB) - ΗΠΑ

- 1,485 ασθενείς με SLE vs 2,775 μη Φλεγμ. Μυοσκελ. Παθήσεις
- Ηλικία: (ΣΕΛ) 48.3 vs. (μηΦΜΠ) 64.9
- Χρονιότητα νόσου: (ΣΕΛ) 13 vs (μηΦΜΠ) 14 έτη

Figure: Sex-adjusted relative incidence of incident herpes zoster by age for each diagnosis



- ✓ age-adjusted incidence: 12.0 ΣΕΛ vs 8.7 μηΦΜΠ ανά 1000 ασθενο-έτη
- ✓ HR (για ΣΕΛ) 1.7 (95% CI 1.08-2.71)
- ✓ Παράγοντες κινδύνου:
  - ➢ prednisone (HR 2.29, 95% CI 1.24-4.23)
  - ➢ mycophenolate mofetil (HR 5.00, 95% CI 1.40-17.6)

Οι ασθενείς με ΣΕΛ είχαν πολύ χαμηλότερο ποσοστό εμβολιασμού για ΕΖ: 7.1% ΣΕΛ vs. 13% μηΦΜΠ, p<0.001.

ΣΕΛ και κίνδυνος ΕΖ

Epidemiology and outcomes

LUPUS SCIENCE & MEDICINE

Herpes zoster in SLE: prevalence, incidence and risk factors

Toronto Lupus Clinic – Καναδάς

Andrew Kwan,[1] Hanan Al Rayes,[2] Tijana Lazova,[3] Nicole Anderson,[4] Dennisse Bonilla,[4] Jiandong Su,[4] Zahi Touma [1,5]

- 422 ασθενείς
- 2016 - 2018
- Ερωτηματολόγιο
- Επιβεβαίωση από θεράποντα ιατρό

✓ Παράγοντες κινδύνου:
- ➢ SLEDAI-2KG
- ➢ Κορτικοστεροειδή
- ➢ Λεμφοπενία

Table 4 Time-dependent survival analyses using three regression models with SLEDAI-2K, SLEDAI-2KG and SLEDAI organ systems

		Univariable cox regression		Multivariable analysis with SLEDAI-2K		Multivariable analysis with SLEDAI-2KG	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Demographics	Female sex	1.89 (0.69 to 5.17)	0.22	2.41 (0.76 to 7.67)	0.13	2.51 (0.79 to 7.98)	0.12
	Age at SLE diagnosis	1.00 (0.98 to 1.02)	0.77				
	Age at first visit	1.00 (0.98 to 1.02)	0.73				
	Caucasian	1.46 (0.89 to 2.38)	0.13			1.41 (0.85 to 2.32)	0.18
Study protocol	SLEDAI-2KG at each visit	1.21 (1.10 to 1.33)	<0.0001			1.178 (1.06 to 1.31)	0.002
	SLEDAI-2K at each visit	1.06 (1.02 to 1.11)	0.004	1.04 (0.99 to 1.09)	0.11		
	SDI score	0.87 (0.72 to 1.10)	0.14	0.84 (0.69 to 1.02)	0.10	0.84 (0.69 to 1.02)	0.09
	Fibromyalgia	0.94 (0.48 to 1.85)	0.86				
Treatment	Glucocorticoid Use	1.66 (1.04 to 2.66)	0.03			Not entered into multivariable analysis, part of SLEDAI-2KG	
	Glucocorticoid dose (mg/day)	1.02 (1.01 to 1.02)	0.0001	1.01 (1.001 to 1.02)	0.03		
	Antimalarial	1.19 (0.75 to 1.90)	0.46				
	Treated with Immunosuppressives	1.52 (0.98 to 2.36)	0.06				
Laboratory markers	Antiphospholipid antibody at any time	0.94 (0.48 to 1.85)	0.86				
	Leucopenia (WBC<4.0*10^9/L)	1.27 (0.51 to 3.2)	0.60				
	Neutropenia (<1.5* 10^9)	0.83 (0.40 to 1.73)	0.62				
	Lymphopenia (<1.0* 10^9)	1.78 (1.12 to 2.80)	0.01	1.63 (1.02 to 2.59)	0.041	1.56 (0.98 to 2.49)	0.06
	Anaemia	1.25 (0.78 to 2.02)	0.36				
	Low IgA	1.52 (0.21 to 10.10)	0.68				
	Low IgG	1.61 (0.39 to 6.58)	0.51				
	Low IgM	1.12 (0.35 to 3.55)	0.85				

*All of the above variables were time-dependent with the exception of: female sex, age at SLE diagnosis, age at first visit and Caucasian ethnicity.
*In the third multivariable regression model with SLEDAI organ systems, lymphopenia was the only statistically significant predictor of HZ events (HR=1.64, 95% CI 1.03 to 2.95, p=0.037), the other adjusted variables in the model included SLEDDAI-2K organ systems, SDI and glucocorticoid dose which did not sustain significance. As a result this was not included in the above table.
HZ, herpes zoster; SLEDAI-2K, SLEDAI-2K, SLE Disease Activity Index 2000; SLEDAI-2KG, SLEDAI-2K Glucocorticoid Index; WBC, white blood cells.

Kwan A, Rayes HA, Lazova T, et al.. Lupus Science & Medicine 2022;9:e000574.

ΣΕΛ και κίνδυνος ΕΖ

Paper

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Prevalence and risk factors of herpes zoster infection in patients with biopsy proven lupus nephritis undergoing immunosuppressive therapies

Τριτοβάθμιο Νοσοκομείο – Κίνα

Chi Chiu Mok, Sau Mei Tse, Kar Li Chan and Ling Yin Ho

- 251 ασθενείς με ***νεφρική προσβολή (βιοψία)***
- 2004 – 2018 (Αναδρομική μελέτη)
- Follow up 24 μήνες (maintenance therapy)
- 8.84/100 patient-years

✓ Παράγοντες κινδύνου:
- SLEDAI
- Κορτικοστεροειδή
- 1ο επεισόδιο νεφρίτιδας

➢ Θεραπευτικό σχήμα:
- MMF
- CYC

❖ ***Στη μέγιστη δόση***

Clinical parameters	HZ infection with 24 months of therapy, episodes		
	At induction phase $n = 23$	At maintenance phase $n = 32$	p
	Mean ± SD; number (%)		
Age at renal biopsy, years	32.7 ± 13.0	38.3 ± 14.0	0.14
Female sex	22 (96)	29 (91)	0.63
Histological class III/IV	19 (83)	24 (75)	0.74
Body weight at renal biopsy, kg	52.7 ± 11.8	55.8 ± 11.0	0.32
Clinical renal SLEDAI	5.2 ± 2.5	2.0 ± 2.5	<0.001
Clinical non-renal SLEDAI	2.0 ± 3.0	0.2 ± 0.8	0.01
Total SLEDAI	9.8 ± 5.8	4.3 ± 3.0	<0.001
Daily prednisolone dose, mg	24.3 ± 12.9	7.6 ± 3.3	<0.001
Total WBC count, $\times 10^9$/L	5.81 ± 2.88	6.03 ± 2.42	0.78
Neutrophil count, $\times 10^9$/L	3.88 ± 1.92	4.86 ± 2.37	0.13
Lymphocyte count, $\times 10^9$/L	1.33 ± 0.93	0.98 ± 0.95	0.20
C3, g/L	0.61 ± 0.33	0.82 ± 0.21	0.01
C4, g/L	0.15 ± 0.11	0.17 ± 0.07	0.40
Anti-dsDNA, IU/mL	185 ± 125	106 ± 105	0.02
Serum albumin, g/L	29.8 ± 8.5	37.3 ± 6.3	0.001
Serum globulin, g/L	29.5 ± 6.6	30.7 ± 5.1	0.47

HZ: herpes zoster; SD: standard deviation; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; eGFR: estimated glomerular filtration rate; Ig: immunoglobulin; WBC: white blood cell.

Covariates	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Age, per year	1.004 (0.98–1.03)	0.68	1.02 (0.99–1.05)	0.07
Male sex	0.80 (0.26–2.40)	0.68	0.92 (0.29–2.92)	0.88
First time renal disease	2.26 (1.16–4.42)	0.02	2.25 (1.08–4.71)	0.03
Class III/IV disease	1.75 (0.88–3.49)	0.11	1.35 (0.57–3.18)	0.49
Total SLEDAI score	1.03 (0.99–1.09)	0.17	1.01 (0.95–1.07)	0.77
Refractory disease at six months	1.63 (0.77–3.47)	0.20	1.67 (0.74–3.78)	0.22
Maximum prednisolone dose, per mg/kg	2.71 (1.02–7.17)	0.045	2.75 (0.82–9.22)	0.10
Maximum MMF dose, per gram	1.15 (0.87–1.52)	0.34	1.84 (1.10–3.07)	0.02
Maximum tacrolimus dose, per milligram	0.99 (0.87–1.15)	0.98	1.24 (0.98–1.56)	0.07
Maximum AZA dose, per milligram	0.99 (0.99–1.01)	0.81	1.01 (0.99–1.03)	0.19
Cumulative CYC dose, per gram	1.05 (0.97–1.13)	0.26	1.14 (1.01–1.28)	0.04

OR: odds ratio; CI: confidence interval; SLEDAI: Systemic Lupus Erythematosus Disease Activity Score; MMF: mycophenolate mofetil; AZA: azathioprine; CYC: cyclophosphamide.

Mok CC et al. Lupus 0 (0) 1-9

ΣΕΛ και κίνδυνος ΕΖ

Belimumab

Lupus

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Long-term open-label continuation study of the safety and efficacy of belimumab for up to 7 years in patients with systemic lupus erythematosus from Japan and South Korea

Yoshiya Tanaka [1], Sang-Cheol Bae [2], Damon Bass [3], Paula Curtis [4], Myron Chu [3], Kathleen DeRose [3], Beulah Ji [4], Regina Kurrasch [3], Jenny Lowe [4], Paige Meizlik [3], David A Roth [3]

Open label phase IV of 2 approval studies of Belimumab

- Κορέα – Ιαπωνία
- 142 ασθενείς
- 4.9% ασθενών με ΣΑΕ
- ΕΖ 3η συχνότερη ανεπιθύμητη ενέργεια
- EAIR 5.9

- *FDA report (Ιουνιος 2022) για AE*
- *14,100 ασθενείς με AE σε Belimumab - 132 (0.94%) EZ*

Anifrolumab

Clinical trials and drug discovery

LUPUS SCIENCE & MEDICINE

Safety profile of anifrolumab in patients with active SLE: an integrated analysis of phase II and III trials

Raj Tummala,[1] Gabriel Abreu,[2] Lilia Pineda,[1] M Alex Michaels,[1] Rubana N Kalyani,[1] Richard A Furie,[3] Eric F Morand[4]

MUSE / TULIP 1,2 studies of Anifroluumab

- ***EAIR risk difference (95%CI) 5.4 (2.8 to 8.4) for HZ***

Table 3 Herpes zoster events in patients during treatment with anifrolumab 300 mg versus placebo in pooled MUSE, TULIP-1 and TULIP-2 data

	Anifrolumab 300 mg (n=459) n (%)	EAIR (per 100 PY)	Placebo (n=466) n (%)	EAIR (per 100 PY)	EAIR (per 100 PY) risk difference (anifrolumab 300 mg – placebo) (95% CI)
Any AE	28 (6.1)	6.9	6 (1.3)	1.5	5.4 (2.8 to 8.4)
Any AE with outcome of death	0	0	0	0	0
Any SAE	2 (0.4)	0.5	0	0	0.5 (–0.5 to 1.7)
Any DAE	2 (0.4)	0.5	0	0	0.5 (–0.5 to 1.7)
Any AE by maximum reported intensity					
Mild	9 (2.0)	2.2	1 (0.2)	0.3	-
Moderate	17 (3.7)	4.1	5 (1.1)	1.2	-
Severe	2 (0.4)	0.5	0	0	-

EAIR was reported per 100 PY and defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time was defined as the time from the date of first administration of investigational product to the date of first event, death, end of treatment plus 28 days or end of study, whatever came first.
AE, adverse event; DAE, AE leading to discontinuation of investigational product; EAIR, exposure-adjusted incidence rate; PY, patient-years; SAE, serious AE.

Tanaka Y, Bae S-C, Bass D, et al.. RMD Open 2021;7:e001629
Tummala R, Abreu G, Pineda L, et al..Lupus Science & Medicine 2021;8:e000464

ΣΕΛ και κίνδυνος ΕΖ

2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

Victoria Furer,[1,2] Christien Rondaan,[3] Marloes W Heijstek,[4] Nancy Agmon-Levin,[5] Sander van Assen,[6] Marc Bijl,[7] Ferry C Breedveld,[8] Raffaele D'Amelio,[9] Maxime Dougados,[10] Meliha Crnkic Kapetanovic,[11] Jacob M van Laar,[12] A de Thurah,[13] Robert BM Landewé,[14,15] Ann [illegible][16] [illegible][17] Karen Schreiber,[18] Leo Smolar,[19] Jim Walker,[20] Ori Elkayam[23]

Recommendation	Infection rate	Efficacy	Immuno-genicity	Safety	SoR*	Level of agreement: average/ range (0–10), %≥8
5. Herpes zoster vaccination may be considered in high-risk patients with AIIRD.	2b	2b	2b	4	B	9.1 7–10 93%

	Overarching principles	Level of Agreement (%)
1.	The vaccination status and indications for further vaccination in patients with AIIRD should be assessed yearly by the rheumatology team.	100%
2.	The individualised vaccination programme should be explained to the patient by the rheumatology team, providing a basis for shared decision-making, and be jointly implemented by the primary care physician, the rheumatology team and the patient.	94%
3.	Vaccination in patients with AIIRD should preferably be administered during quiescent disease.	94%
4.	Vaccines should preferably be administered prior to planned immunosuppression, in particular B cell depleting therapy.	100%
5.	Non-live vaccines can be administered to patients with AIIRD also while treated with systemic glucocorticoids and DMARDs.	100%
6.	Live-attenuated vaccines may be considered with caution in patients with AIIRD.	53%

AIIRD, autoimmune inflammatory rheumatic diseases; DMARDs, disease-modifying antirheumatic drugs.

- "The live attenuated vaccine is preferably administered 4 weeks prior to initiation of bDMARDs or tsDMARDs, but not during the treatment with bDMARDs or tsDMARDs"

  "In patients with uncertain varicella exposure, evaluation of varicella zoster serostatus may be considered before the administration of live-attenuated HZ vaccine in order to prevent primary varicella infection"

- "A new non-live recombinant subunit adjuvant zoster vaccine called Shingrix was licensed in Europe since March 2018"

  "…recommended for adults 50 years and older, including immunosuppressed patients

  "…has been shown to be safe and more efficacious compared with live-attenuated vaccine in elderly adults"

Furer V, et al. Ann Rheum Dis 2019;0:1–14

Συμπερασματικά

- Οι Ρευματοπαθείς ασθενείς διατρέχουν αυξημένο κίνδυνο για ΕΖ σε σχέση με τον γενικό πληθυσμό (κυρίως ΡΑ, ΣΕΛ)
- Ο κίνδυνος είναι αυξημένος ανεξάρτητα με την ηλικία, αλλά αυξάνεται περισσότερο με αυτη
- *Η θεραπευτική παρέμβαση φαίνεται να αυξάνει τον κίνδυνο*
- *Η χορήγηση κορτικοστεροειδών είναι ο σημαντικότερος παράγοντας κινδύνου*
- Οι βιολογικοί παράγοντες ίσως αυξάνουν των κίνδυνο σε κάποια νοσήματα περισσότερο από τα συμβατικά τροποποιητικά της νόσου φάρμακα

- Στον ΣΕΛ: MMF, TAC και CYC αυξάνουν περισσότερο τον κίνδυνο (μέγιστη δόση) + ANFR

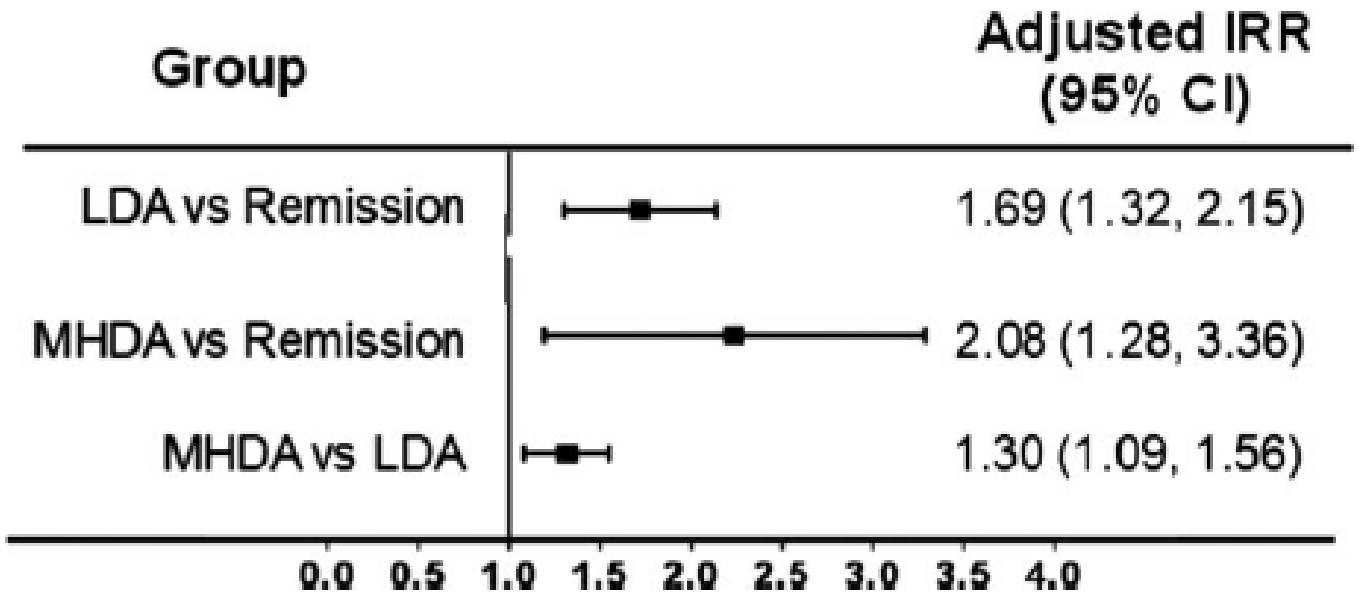
➢ *Στην ΡΑ: JAKi αυξάνουν περισσότερο τον κίνδυνο και ακολουθούν IL6i και B-cell depletion*

➢ *Στην ΨΑ: οι JAKi και οι TNFi ίσως αυξάνουν περισσότερο τον κίνδυνο σε σχέση με IL17/23i, αλλά χρειάζονται περισσότερα δεδομένα*

➢ *Ο πληθυσμός των ρευματοπαθών είναι "υπο-εμβολιασμένος" για τον ΕΖ*

Ευχαριστώ!

Η ύφεση και η χαμηλή ενεργότητα συσχετίστηκαν με χαμηλότερο ποσοστό σοβαρών λοιμώξεων
Retrospective analysis of data from the CORRONA RA registry



The adjusted rate of serious infections was 69% higher in patients in sustained low disease activity (LDA) compared with patients in sustained remission

Accortt et al.,Arthritis Care & Research Vol. 70, No. 5, May 2018, pp 679–684

1998 ως σήμερα...

- Προσοχή σε ευκαιριακές λοιμώξεις (βακτηριακές, ιογενείς, μυκητιασικές
- Αυξημένος κίνδυνος θρομβοεμβολικών επεισοδίων
- Αυξημένη επίπτωση αναζωπύρωση έρπητα ζωστήρα

Rituximab (Μυκητιασικές λοιμώξεις)

TNFα αναστολείς (Λιστέρια - Λεγεωνέλλα)

TNFα αναστολείς (Μυκητιασικές λοιμώξεις)

TNFα αναστολείς (Λεμφοϋπερπλαστική νόσος)

TNFα αναστολείς (Φυματίωση)

Tocilizumab (βακτηριακές, ιογενείς, μυκητιασικές λοιμώξεις)

Abatacept (αντιδράσεις έγχυσης)

Tocilizumab (διάτρηση γαστρεντερικού σωλήνα)

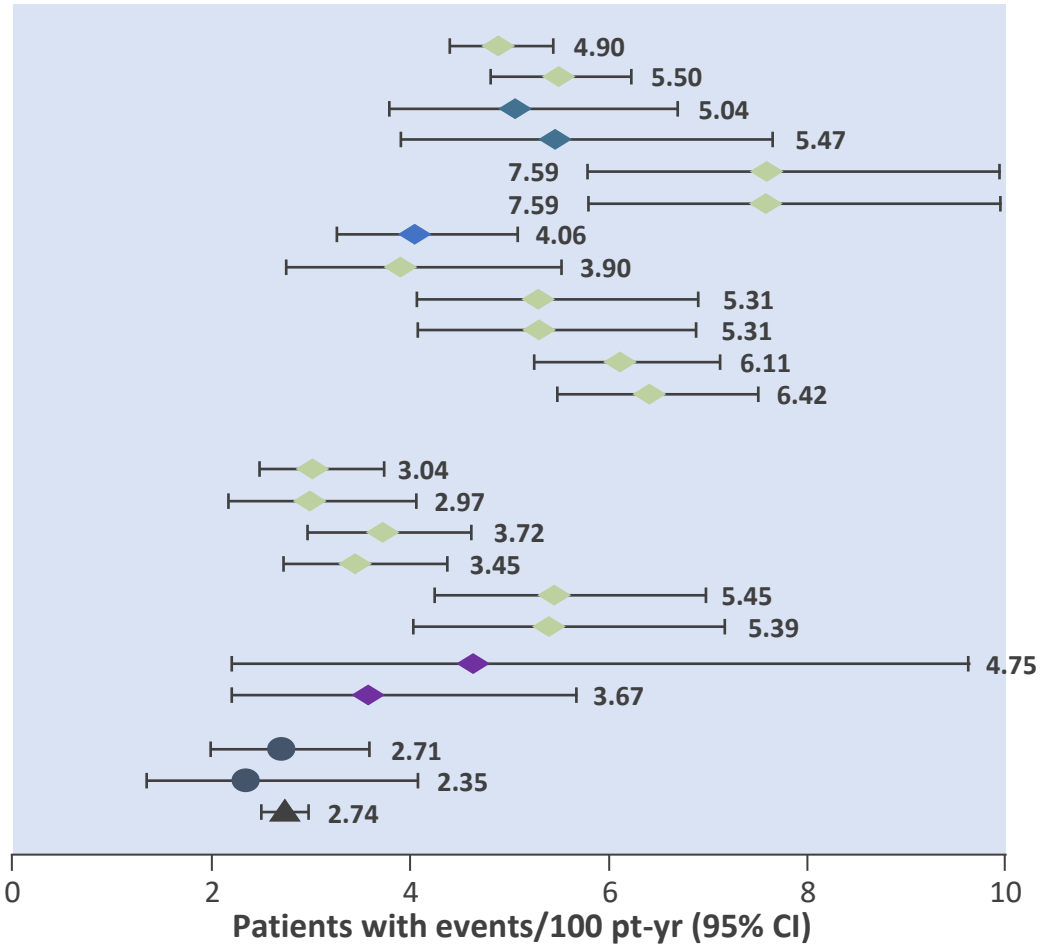
Rituximab (PML)

Rituximab (Αναζωπύρωση HBV)

Rituximab (αντιδράσεις έγχυσης-σύνδρομο λύσης όγκων)

Πoσoστά επίπτωσης για σοβαρή λοίμωξη σε ασθενείς με PA υπό θεραπεία με bDMARDs and JAKi σε RCTs και LTE μελέτες

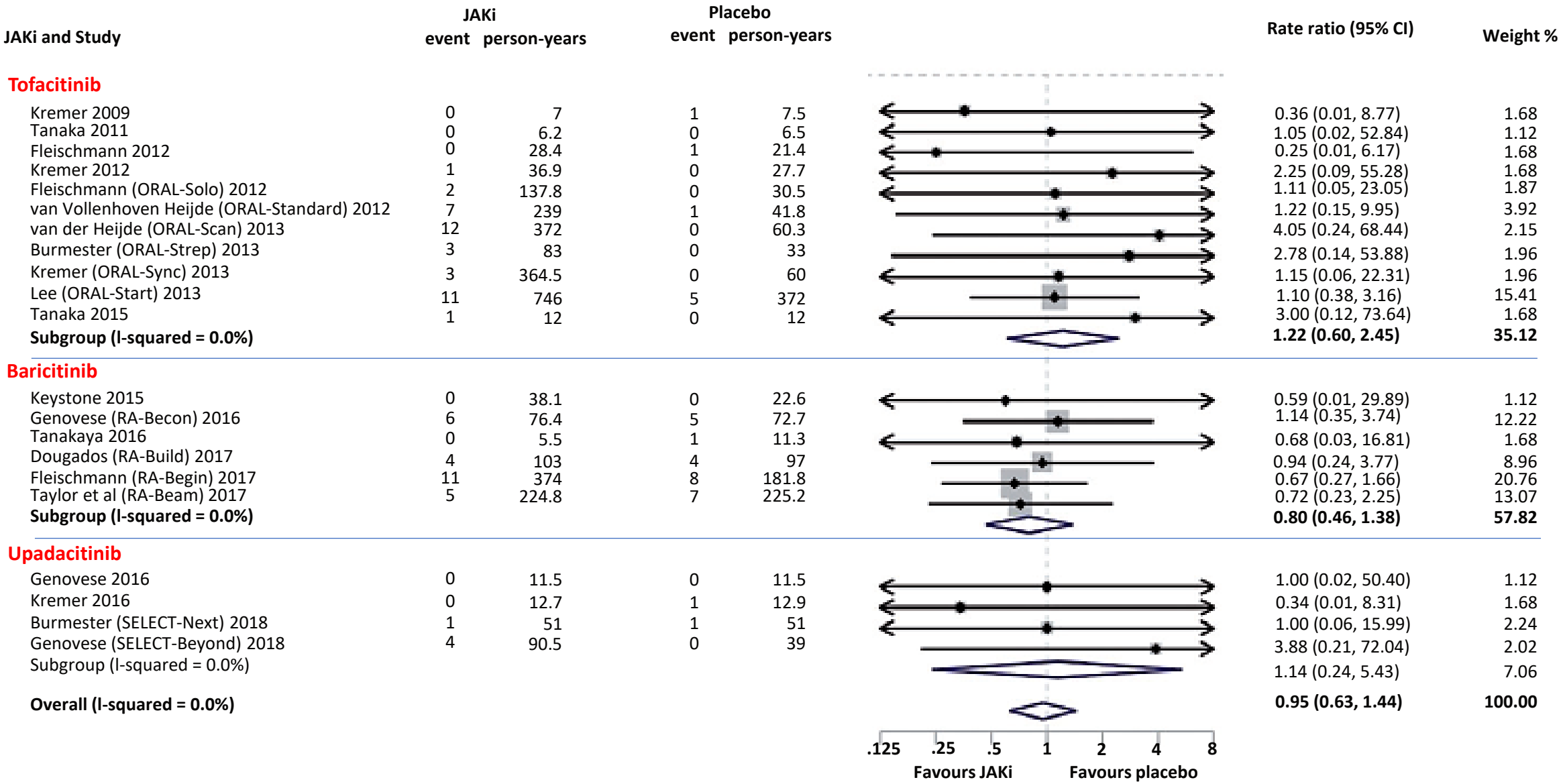
Drug[1,2]		No. trials[2]	Incidence rate (95% CI), per 100 pt yr[1,2]	No. of patients[2]
TNF inhibitors	RCT+LTE	57	4.90	26492
	RCT		5.50	
Adalimumab	RCT+LTE	18	5.04	6570
	RCT		5.47	
Certolizumab pegol	RCT+LTE	5	7.59	3212
	RCT		7.59	
Etanercept	RCT+LTE	17	4.06	7141
	RCT		3.90	
Golimumab	RCT+LTE	6	5.31	2820
	RCT		5.31	
Infliximab	RCT+LTE	11	6.11	4592
	RCT		6.42	
Non-TNF bDMARDs				
Abatacept	RCT+LTE	18	3.04	5953
	RCT		2.97	
Rituximab	RCT+LTE	8	3.72	2926
	RCT		3.45	
Toclizumab	RCT+LTE	13	5.45	5547
tsDMARDs	RCT		5.39	
Baricitinib	2 mg QD	6	4.75	1657
	4 mg QD	6	3.67	3546
Tofacitinib 5 mg BID	RCT[a]	15	2.71	2989
	RCT[b]		2.35	
Tofacitinib all doses	RCT+LTE	17	2.74	6194



- a Estimate from pooled patient-level data
- b Estimate from random-effects meta-analytic model
- CI, confidence interval; BID, twice daily; bDMARD, biologic DMARD; DMARD, disease-modifying anti-rheumatic drug; JAKi, janus kinase inhibitor; LTE, long-term extension;ptyr, patient year; QD, once daily; RA, rheumatoid arthritis, RCT, randomised controlled trial; TNF, tumour necrosis factor; tsDMARD, targeted synthetic DMARD.

1. Strand V et al. Arthritis Res Ther 2015; 17: 362.
2. Strand V et al. Poster THU0211. Presented at EULAR 2017.

Σοβαρές λοιμώξεις σε ασθενείς με ΡΑ υπό θεραπεία με JAK αναστολείς



- CI, confidence interval, JAKi, Janus kinase inhibitor; RA, rheumatoid arthritis.

- Bechman et al Rheumatology 2019;58:1755-766