Safety TsDMARDs nel paziente reumatico anziano

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Agenda

- Safety Small molecules in AR e PsA
- Rischio infettivo
- Rischio cardiovascolare
- Rischio neoplastico
- Rischio/beneficio real world experience

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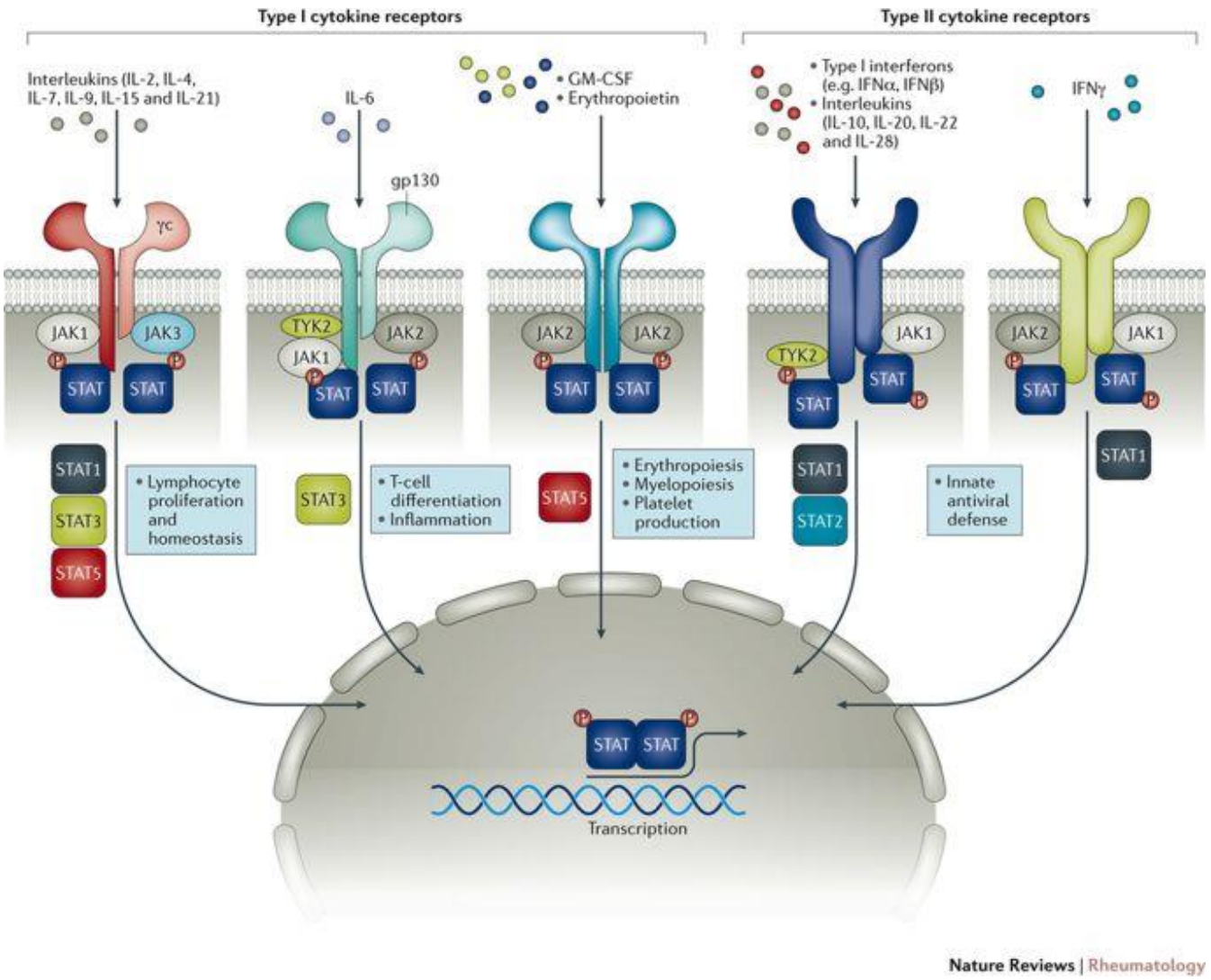
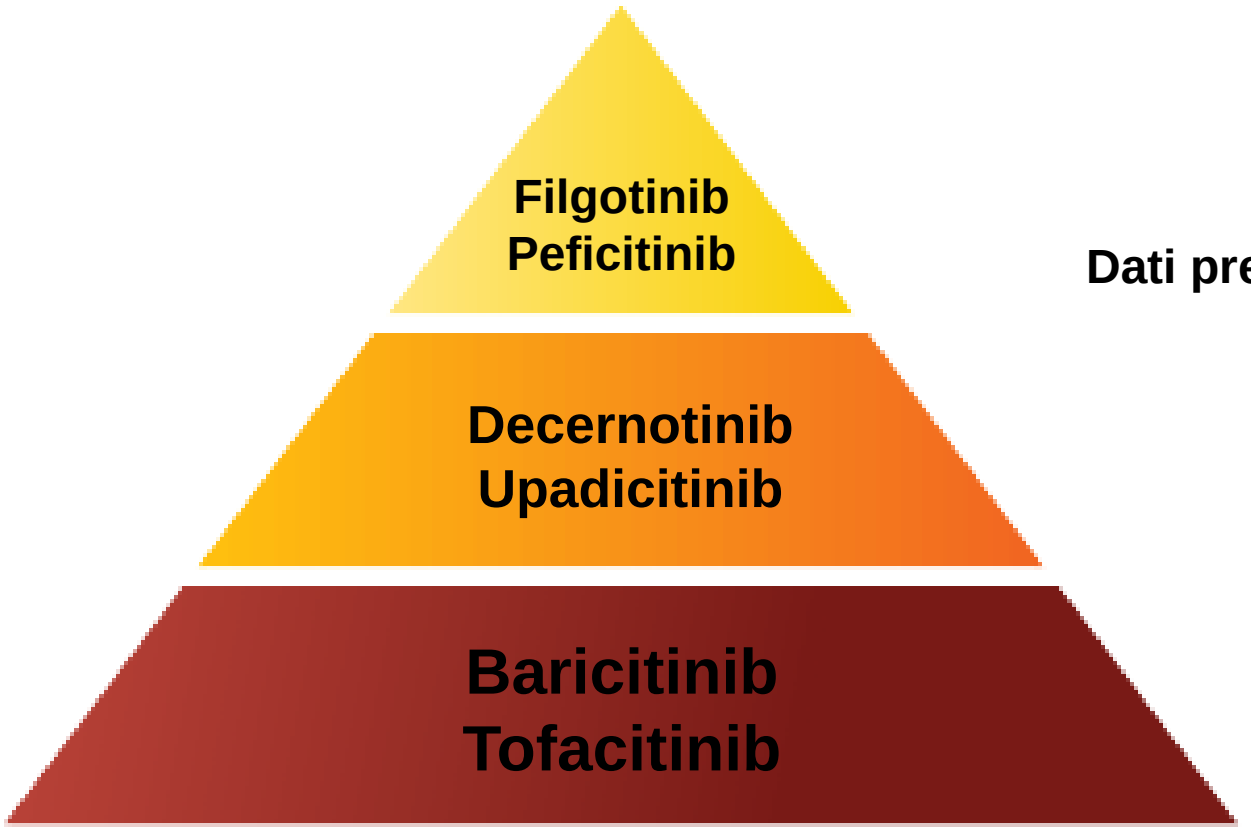
Pathway di segnalazione JAK/STAT



K.L. Winthrop, Nature Reviews Rheumatology 2017

JAK FAMILY AR



Dati preliminari di efficacia

Profilo di sicurezza
ed efficacia

Inibitori fosfodiesterasi 4/JaK PSA

- Apremilast per PSA / psoriasi
- Tofacitinib

EXTENDED REPORT

Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials

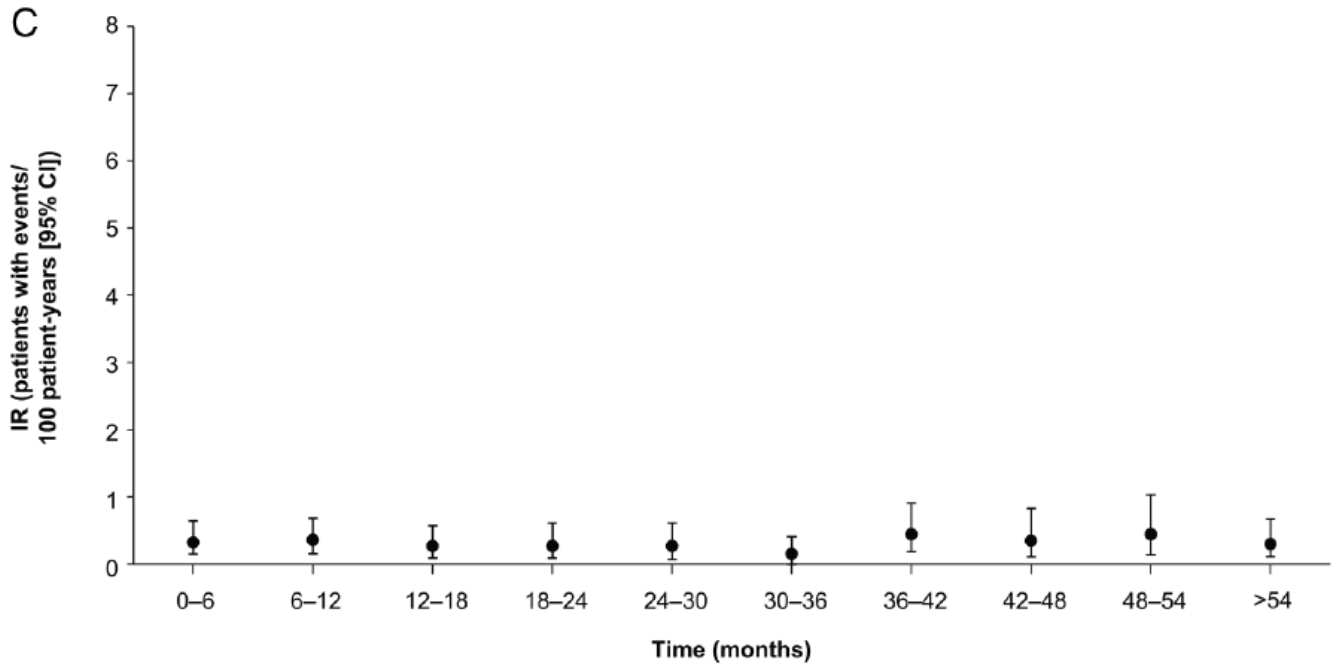
Stanley B Cohen,[1] Yoshiya Tanaka,[2] Xavier Mariette,[3] Jeffrey R Curtis,[4] Eun Bong Lee,[5] Peter Nash,[6] Kevin L Winthrop,[7] Christina Charles-Schoeman,[8] Krishan Thirunavukkarasu,[9] Ryan DeMasi,[10] Jamie Geier,[10] Kenneth Kwok,[10] Lisy Wang,[11] Richard Riese,[11] Jürgen Wollenhaupt[12]

Table 2 IRs (patients with events/100 patient-years; 95% CI) of AEs and SAEs (all-cause)

	All tofacitinib doses N=6194	Average tofacitinib 5 mg twice daily* N=2239	Average tofacitinib 10 mg twice daily* N=3955	Constant tofacitinib 5 mg twice daily† N=2342	Constant tofacitinib 10 mg twice daily† N=2814
Total patient-years of exposure, years	19 406	6870	12 536	3623	6702
Median patient-years of exposure	3.4	3.0	3.5	1.0	2.0
AEs (n=5545)	136.9 (133.3 to 140.5)	136.1 (130.2 to 142.3)	137.3 (132.8 to 141.8)	153.1 (146.1 to 160.4)	157.9 (151.7 to 164.3)
Discontinuations due to AEs (n=1446)	7.5 (7.1 to 7.8)	8.6 (7.9 to 9.3)	6.8 (6.4 to 7.3)	7.2 (6.4 to 8.2)	7.8 (7.1 to 8.5)
SAEs (n=1649)	9.4 (9.0 to 9.9)	10.1 (9.4 to 11.0)	9.1 (8.5 to 9.7)	9.2 (8.2 to 10.3)	9.3 (8.6 to 10.1)
Mortality‡ (n=51)	0.3 (0.2 to 0.3)	0.4 (0.3 to 0.6)	0.2 (0.1 to 0.3)	0.3 (0.2 to 0.5)	0.2 (0.1 to 0.3)

*Average dosing was based on average daily dose: patients receiving <15 mg/day were assigned to the 5 mg twice daily group; patients receiving ≥15 mg/day were assigned to the 10 mg twice daily group.
†Constant dosage without prior exposure to another tofacitinib dose or adalimumab during the study; patients who switched doses were not included in this group.
‡Within 30 days of last dose of study drug.
AE, adverse event; IR, incidence rate; n, unique number of patients with event; SAE, serious AE.

S. Cohen et Al., 2017



	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	>54
Total patient exposure, n	6,194	5,305	4,846	4,446	4,137	3,675	3,409	3,024	2,637	1,998
Patients with OI, n	10	9	6	6	5	2	7	5	5	6
Total patient-year exposure for event	2,810.1	2,494.9	2,272.6	2,117.1	1,901.9	1,738.5	1,583.0	1,395.4	1,125.7	1,932.3
IR, patients with events/100 patient-years (95% CI)	0.4 (0.2–0.7)	0.4 (0.2–0.7)	0.3 (0.1–0.6)	0.3 (0.1–0.6)	0.3 (0.1–0.6)	0.1 (0.0–0.4)	0.4 (0.2–0.9)	0.4 (0.1–0.8)	0.4 (0.1–1.0)	0.3 (0.1–0.7)

S. Cohen et Al., 2017

Machado et al. Arthritis Research & Therapy (2018) 20:60
https://doi.org/10.1186/s13075-018-1539-6

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Proportion of patients who achieved therapy effectiveness and individual criteria at 1 year of follow-up (n=16,305)

Effectiveness and safety of tofacitinib in rheumatoid arthritis: a cohort study

Marina Amaral de Ávila Machado[1], Cristiano Soares de Moura[1], Steve Ferreira Guerra[1], Jeffrey R. Curtis[2], Michal Abrahamowicz[1,3] and Sasha Bernatsky[1,3*]

Effectiveness criteria	DMARDs		TNFi ± DMARDs		Non-TNF biologics ± DMARDs		Tofacitinib ± DMARDs	
	Percent	95% CI	Percent	95% CI	Percent	95% CI	Percent	95% CI
Effective therapy (satisfied all six criteria)	11.1	10.1–12.1	18.6	17.9–19.4	19.8	18.2–21.4	15.4	6.6–24.2
Criterion 1 High adherence	26.6	25.1–28.0	44.0	43.0–44.9	53.3	51.3–55.3	27.7	16.8–38.6
Criterion 2 No biologic or tofacitinib switch or addition	72.7	71.2–74.1	64.3	63.4–65.2	82.1	80.5–83.6	84.6	75.8–93.4
Criterion 3 No DMARD switch or addition	85.3	84.2–86.5	96.1	95.8–96.5	95.5	94.6–96.3	98.5	95.5–100
Criterion 4 No increase in dose or frequency of index drug	92.0	91.1–92.9	94.0	93.5–94.4	88.9	87.6–90.1	100.0[a]	–
Criterion 5 No more than one glucocorticoid joint injection	91.3	90.3–92.2	88.8	88.2–89.4	72.8	71.0–74.6	87.7	79.7–95.7
Criterion 6 No new/increased oral glucocorticoid dose	81.4	80.2–82.7	83.3	82.6–84.1	78.0	76.3–79.7	76.9	66.7–87.2

DMARD Disease-modifying antirheumatic drug, *TNFi* Tumor necrosis factor inhibitors

[a]Standard tofacitinib dose is usually not increased

- Machado et al. Arthritis Research & Therapy (2018) 20:60

Efficacy and safety of tofacitinib in older and younger patients with rheumatoid arthritis

J.R. Curtis[1], H. Schulze-Koops[2], L. Takiya[3], C.A. Mebus[4], K.K. Terry[4], P. Biswas[3], T.V. Jones[3]

[1]University of Alabama at Birmingham, Birmingham AL, USA; [2]Division of Rheumatology and Clinical Immunology, Department of Medicine IV, University of Munich, Munich Germany; [3]Pfizer Inc, Collegeville, PA, USA; [4]Pfizer Inc, Groton, CT, USA.

Table I. Demographic data and baseline clinical characteristics in five Phase 3 and two long-term extension studies of tofacitinib, by age group (<65 years and ≥65 years) and treatment.

	Phase 3 studies						LTE studies			
	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Placebo		Tofacitinib 5 mg BID		Tofacitinib 10 mg BID	
	<65 years (n=1026)	≥65 years (n=190)	<65 years (n=1030)	≥65 years (n=184)	<65 years (n=580)	≥65 years (n=101)	<65 years (n=1189)	≥65 years (n=232)	<65 years (n=2252)	≥65 years (n=429)
Female (%)	84.8	82.6	85.0	84.8	82.1	76.2	84.5	78.0	83.3	80.2
Age, mean (range)	50.1 (18.0–64.0)	70.2 (65.0–86.0)	49.5 (18.0–64.0)	69.2 (65.0–85.0)	49.4 (18.0–64.0)	70.1 (65.0–82.0)	49.6 (18.0–64.0)	69.3 (65.0–81.0)	50.4 (18.0–64.0)	69.5 (65.0–86.0)
Ethnicity (%)										
Caucasian	58.3	73.2	59.3	70.7	62.2	77.2	43.7	56.5	67.0	79.2
Black	3.9	2.6	2.6	4.3	3.8	2.0	1.6	1.3	3.7	3.0
Asian	28.7	17.4	27.5	16.8	26.2	13.9	45.7	36.2	20.2	12.5
Other	9.2	6.8	10.6	8.2	7.8	6.9	9.0	6.0	9.1	5.3
Geographical location (%)										
US/Canada	215 (21.0)	51 (26.8)	218 (21.2)	57 (31.0)	361 (62.2)	32 (21.7)	156 (13.1)	42 (18.1)	703 (31.3)	149 (34.7)
Europe	323 (31.5)	82 (43.2)	331 (32.1)	67 (36.4)	22 (3.8)	44 (43.6)	269 (22.6)	71 (30.6)	744 (33.1)	179 (41.7)
Latin America	173 (16.9)	16 (8.4)	165 (16.0)	20 (10.9)	152 (26.2)	9 (8.9)	227 (19.1)	35 (15.1)	330 (14.7)	29 (6.8)
Asia	315 (30.7)	41 (21.6)	316 (30.7)	40 (21.7)	45 (7.8)	16 (15.8)	537 (45.2)	84 (36.2)	471 (21.0)	72 (16.8)
Concomitant corticosteroids (%)	57.3	54.7	55.8	52.7	56.4	47.5	53.7	51.7	50.0	50.1
No. prior bDMARDs (mean)	1.6	1.5	1.5	1.7	1.6	1.6	1.0	1.0	1.3	1.0
≥1 cardiac disorder (%)	5.2	16.8	6.7	19.0	6.4	14.9	4.3	13.8	6.5	17.5
Diabetes (%)	7.7	15.3	7.2	15.8	5.9	13.9	4.4	11.6	6.2	9.8
Smoking status (%)										
Never smoked	67.3	61.6	65.6	71.7	62.9	59.4	63.0	62.9	62.3	62.5
Smoker	14.7	7.9	19.8	4.3	20.0	13.9	18.3	10.3	19.4	10.3
Ex-smoker	17.9	30.5	14.6	23.9	16.7	26.7	13.4	22.0	18.0	27.0
Missing	–	–	–	–	<1.0	–	5.3	4.7	<1.0	<1.0

bDMARDs: biologic disease-modifying anti-rheumatic drugs; BID: twice daily; LTE: long-term extension.

Curtis et al, 2017

RMD Open
Rheumatic & Musculoskeletal Diseases

SHORT REPORT

Safety and efficacy of baricitinib in elderly patients with rheumatoid arthritis

Roy Fleischmann,[1] Jahangir Alam,[2] Vipin Arora,[2] John Bradley,[2] Douglas E Schlichting,[2] David Muram,[2] Josef S Smolen[3]

Table 1 Baseline demographic and disease characteristics

	<50 years		≥50 and <65 years		≥65 years	
	Placebo (n=254)	Baricitinib 4 mg (n=259)	Placebo (n=349)	Baricitinib 4 mg (n=319)	Placebo (n=113)	Baricitinib 4 mg (n=136)
Age	39.7 (7.5)	40.0 (7.2)	56.9 (4.3)	56.5 (4.0)	69.5 (4.1)	69.6 (4.2)
Female, n (%)	218 (85.8)	214 (82.6)	263 (75.4)	246 (77.1)	90 (79.6)	102 (75.0)
Region						
Asia including Japan, n (%)	72 (28.3)	67 (25.9)	85 (24.4)	88 (27.6)	24 (21.2)	25 (18.4)
Central and South America, Mexico, n (%)	72 (28.3)	72 (27.8)	76 (21.8)	72 (22.6)	21 (18.6)	28 (20.6)
Eastern Europe, n (%)	42 (16.5)	37 (14.3)	58 (16.6)	58 (18.2)	23 (20.4)	25 (18.4)
Western Europe, n (%)	12 (4.7)	13 (5.0)	27 (7.7)	24 (7.5)	15 (13.3)	16 (11.8)
USA and Canada, n (%)	27 (10.6)	34 (13.1)	59 (16.9)	44 (13.8)	21 (18.6)	30 (22.1)
Rest of world, n (%)	29 (11.4)	36 (13.9)	44 (12.6)	33 (10.3)	9 (8.0)	12 (8.8)
Duration of RA*, years	5.9 (5.7)	6.2 (6.1)	8.4 (8.1)	8.6 (8.9)	11.2 (9.6)	9.8 (10.0)
<1 year, n (%)	46 (18.1)	41 (15.9)	49 (14.0)	50 (15.7)	10 (8.9)	22 (16.2)
≥1 to <5 years, n (%)	94 (37.0)	101 (37.1)	111 (31.8)	102 (32.0)	29 (25.9)	30 (22.1)
≥5 to <10 years, n (%)	62 (24.4)	63 (24.4)	79 (22.6)	67 (21.0)	25 (22.3)	36 (26.5)
≥10 years, n (%)	52 (20.5)	53 (20.5)	110 (31.5)	100 (31.3)	48 (42.9)	48 (35.3)
ACPA positive, n (%)	214 (84.3)	208 (80.3)	288 (82.5)	269 (84.3)	94 (83.2)	113 (83.1)
RF positive, n (%)	223 (87.8)	223 (86.1)	304 (87.1)	272 (85.3)	95 (84.1)	117 (86.0)
Swollen joint count of 66	14.0 (8.5)	14.6 (8.2)	15.1 (9.6)	14.6 (7.8)	15.1 (7.4)	14.2 (7.4)
Tender joint count of 68	22.8 (12.6)	23.9 (13.3)	23.9 (14.7)	23.8 (13.4)	24.7 (14.7)	22.9 (13.1)
hsCRP, mg/L	18.1 (18.7)	19.6 (20.9)	20.0 (20.7)	20.3 (20.8)	18.1 (25.2)	18.2 (21.2)
DAS28-hsCRP	5.6 (0.9)	5.7 (0.9)	5.7 (1.0)	5.7 (0.9)	5.6 (0.9)	5.7 (0.9)
DAS28-ESR	6.3 (1.0)	6.3 (0.9)	6.3 (1.0)	6.4 (0.9)	6.4 (1.0)	6.4 (0.9)
CDAI	36.6 (11.7)	37.3 (12.0)	37.0 (13.2)	37.5 (11.8)	37.3 (12.2)	37.9 (11.8)
SDAI	38.4 (12.1)	39.3 (12.6)	39.0 (13.6)	39.5 (12.4)	39.1 (12.8)	39.7 (12.4)
HAQ-DI	1.5 (0.6)	1.5 (0.6)	1.6 (0.7)	1.6 (0.7)	1.6 (0.6)	1.6 (0.7)

Data are mean (SD) unless otherwise noted.
*Time since diagnosis.
ACPA, anti-citrullinated peptide antibody; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score based on 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity C-reactive protein; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simple Disease Activity Index.

Fleishman et. Al, 2018

RHEUMATOLOGY

Rheumatology 2018;57:1253–1263
doi:10.1093/rheumatology/key032
Advance Access publication 4 April 2018

Original article

Apremilast monotherapy in DMARD-naive psoriatic arthritis patients: results of the randomized, placebo-controlled PALACE 4 trial

Alvin F. Wells[1], Christopher J. Edwards[2], Alan J. Kivitz[3], Paul Bird[4], Dianne Nguyen[5], Maria Paris[5], Lichen Teng[5] and Jacob A. Aelion[6]

TABLE 1 Baseline demographic and clinical characteristics: modified intent-to-treat population ($N = 527$)

Characteristics	Placebo ($n = 176$)	Apremilast 20 mg BID ($n = 175$)	Apremilast 30 mg BID ($n = 176$)
Age, mean (S.D.), years	50.5 (11.6)	49.2 (12.0)	48.4 (12.5)
Female, *n* (%)	86 (48.9)	95 (54.3)	96 (54.5)
Race, *n* (%)			
White	174 (98.9)	174 (99.4)	172 (97.7)
Asian	0 (0.0)	1 (0.6)	2 (1.1)
Black	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (1.1)	0 (0.0)	2 (1.1)
Region, *n* (%)			
North America	51 (29.0)	51 (29.1)	53 (30.1)
Europe	83 (47.2)	73 (41.7)	82 (46.6)
Rest of world	42 (23.9)	51 (29.1)	41 (23.3)
Weight, mean (S.D.), kg	82.4 (18.24)	84.5 (22.09)	85.7 (20.60)
BMI, mean (S.D.), kg/m^2	28.7 (5.6)	29.8 (7.2)	29.7 (6.4)
Duration, mean (S.D.), years			
PsA	3.4 (5.1)	3.2 (4.7)	3.6 (5.0)
Psoriasis	16.8 (13.7)	15.3 (12.7)	15.4 (13.3)
PASI score (0–72),[a] mean (S.D.)	6.6 (6.14)	8.3 (7.95)	6.6 (5.11)
Psoriasis BSA $\geqslant 3\%$, *n* (%)	93 (52.8)	104 (59.4)	109 (61.9)

Wells et Al., 2018

SJC (0–76), mean (S.D.)	11.3 (7.6)	11.3 (7.8)	10.9 (8.6)
TJC (0–78), mean (S.D.)	19.6 (13.7)	21.1 (15.1)	19.5 (14.4)
HAQ-DI (0–3), mean (S.D.)	1.0 (0.61)	1.1 (0.59)	1.1 (0.58)
CRP (normal range 0–0.5), mean (S.D.), mg/dl	1.1 (2.7)	0.9 (1.1)	0.8 (1.1)
Pain VAS (0–100), mean (S.D.)	52.8 (21.0)	54.5 (21.6)	52.6 (21.4)
Patient's global assessment of disease activity (0–100 mm VAS), mean (S.D.)	54.0 (21.9)	52.3 (21.1)	53.6 (20.1)
Physician's global assessment of disease activity (0–100 mm VAS), mean (S.D.)	54.3 (18.5)	54.1 (18.8)	51.7 (17.5)
DAS28-CRP, mean (S.D.)	4.6 (1.1)	4.7 (1.1)	4.5 (1.0)
CDAI (0–76), mean (S.D.)	26.5 (11.8)	26.8 (11.7)	25.7 (12.0)
SF-36v2 physical functioning (norm-based), mean (S.D.)	36.1 (10.8)	35.2 (9.9)	35.7 (10.5)
Presence of enthesitis, *n* (%)	115 (65.3)	117 (66.9)	111 (63.1)
Presence of dactylitis, *n* (%)	90 (51.1)	89 (50.9)	84 (47.7)
Baseline use of NSAIDs, *n* (%)	129 (73.3)	123 (70.3)	133 (75.6)
Baseline corticosteroids (mean dose[b] 6.71 mg/day), *n* (%)	12 (6.8)	13 (7.4)	13 (7.4)
Baseline use of opiate analgesic, *n* (%)	8 (4.5)	17 (9.7)	10 (5.7)

n reflects the number of modified intent-to-treat patients; the actual number of patients available for each parameter may vary. [a]Examined among patients with psoriasis involving $\geqslant$3% of BSA at baseline and having a PASI score at baseline (placebo, $n = 93$; apremilast 20mg BID, $n = 104$; apremilast 30mg BID, $n = 107$). [b]All converted to oral prednisone dose. CDAI: Clinical Disease Activity Index; SF-36v2: 36-item Short-Form Health Survey version 2; VAS: visual analogue scale.

Wells et Al., 2018

TABLE 4 AEs and laboratory abnormalities during the placebo-controlled period (weeks 0–24) and apremilast exposure period (weeks 0–52)

Events and Laboratory Assessments	Weeks 0–24[a]			Weeks 0–52[b]	
		Apremilast		Apremilast	
	Placebo ($n=176$)	20 mg BID ($n=175$)	30 mg BID ($n=175$)	20 mg BID ($n=252$)	30 mg BID ($n=252$)
Overview of AEs, *n* (%)					
Any AE	73 (41.5)	87 (49.7)	99 (56.6)	146 (57.9)	157 (62.3)
Any SAE	5 (2.8)	3 (1.7)	1 (0.6)	16 (6.3)	6 (2.4)
Any AE leading to drug withdrawal	4 (2.3)	4 (2.3)	6 (3.4)	14 (5.6)	12 (4.8)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs reported by ⩾5% of patients in any treatment group, *n* (%)					
Nausea	4 (2.3)	16 (9.1)	28 (16.0)	20 (7.9)	34 (13.5)
Diarrhoea	3 (1.7)	12 (6.9)	21 (12.0)	23 (9.1)	28 (11.1)
Headache	4 (2.3)	6 (3.4)	15 (8.6)	8 (3.2)	23 (9.1)
Upper respiratory tract infection	4 (2.3)	6 (3.4)	7 (4.0)	10 (4.0)	15 (6.0)
Select laboratory assessments, *n/m* (%)[c]					
Alanine aminotransferase >150 U/l	2/174 (1.1)	0/173 (0.0)	0/171 (0.0)	1/250 (0.4)	2/246 (0.8)
Creatinine (male >156 μmol/l; female >126 μmol/l)	0/174 (0.0)	1/173 (0.6)	0/171 (0.0)	1/250 (0.4)	1/246 (0.4)
Haemoglobin (male: decrease >2.0 and value <10.5 g/dl; female: decrease >2.0 and value <10.0 g/dl)	0/174 (0.0)	0/173 (0.0)	0/170 (0.0)	1/250 (0.4)	5/245 (2.0)
Leucocytes <2.0, 10^9/l	1/174 (0.6)	0/173 (0.0)	0/171 (0.0)	0/250 (0.0)	1/246 (0.4)
Neutrophils <0.75, 10^9/l	1/174 (0.6)	1/173 (0.6)	1/170 (0.6)	2/250 (0.8)	1/245 (0.4)
Platelets <75, 10^9/l	0/174 (0.0)	0/173 (0.0)	0/170 (0.0)	0/250 (0.0)	0/246 (0.0)

[a]Placebo-controlled period includes data through week 16 for patients who initially received placebo who escaped and data through week 24 for all other patients. [b]Includes all patients who received one or more doses of apremilast, regardless of when treatment started. [c]Represents patients with at least one occurrence of the abnormality (*n*)/patients with a baseline value and at least one post-baseline value for criteria requiring baseline or patients with at least one post-baseline value for criteria not requiring baseline (*m*).

Wells et Al., 2018

Agenda

- Safety Small molecules in AR e PsA
- **Rischio infettivo**
- Rischio cardiovascolare
- Rischio neoplastico
- Rischio/beneficio real world experience

Safety Profile of Baricitinib for the Treatment of Rheumatoid Arthritis up to 5.5 Years: An Updated Integrated Safety Analysis

Genovese et Al., 2017

Table 1. Safety outcomes with up to 5.5 years of exposure to baricitinib

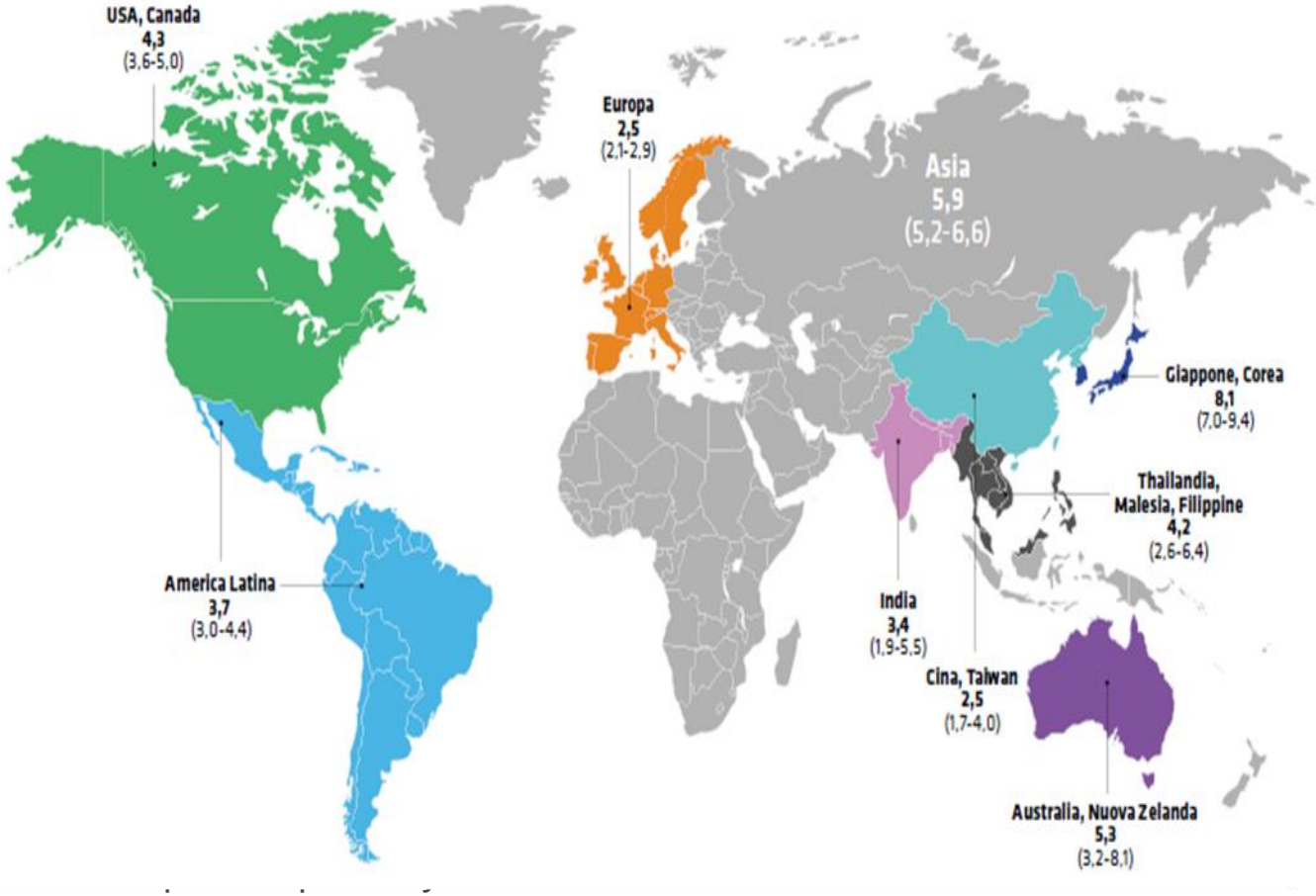
	PBO-bari 4 mg[a] (6 study, to Week 24)		Bari 2 mg-4 mg-extended[b] (4 study, including LTE)		All-bari-RA 01-Sept-2016	All-bari-RA 10-Aug-2015
	PBO	Bari 4 mg	Bari 2 mg	Bari 4 mg	All Bari RA	All Bari RA
Exposure						
Number of patients	1070	997	479	479	3492	3464
Patient-years of exposure	393.8	409.4	554.5	604	6637	4214
Median, days	166	169	257.0	342	760 (2.1 yrs)	--
Longest exposure, days	235	211	1276	1991	2019 (5.5 yrs)	--
Permanent DC due to AE, n (EAIR)	35 (8.9)	47 (11.5)	37 (6.6)	55 (8.9)	393 (5.8)	255 (6.1)
Mortality, n (IR), [95% CI]	2 (0.5) [0.1, 1.8]	3 (0.7) [0.1, 2.1]	1 (0.18) [0.00, 1.0]	3 (0.49) [0.1, 1.4]	22 (0.33) [0.2, 0.5]	13 (0.3)
Malignancy, n (IR), [95% CI]						
Malignancy excluding NMSC	2 (0.5) [0.1, 1.8]	2 (0.5) [0.1, 1.7]	3 (0.5) [0.1, 1.6]	8 (1.3) [0.6, 2.6]	52 (0.8) [0.6, 1.0]	29 (0.7)
	--	--	7 (0.7)[RAN] [0.3, 1.4]	9 (0.9)[RAN] [0.4, 1.6]	--	--
Lymphoma	0	0	0	1 (0.09) [0.002, 0.52]	6 (0.09) [0.03, 0.19]	3 (0.07)
NMSC	1 (0.2) [0.0, 1.4]	3 (0.7) [0.1, 2.1]	2 (0.4) [0.04, 1.3]	6 (1.0) [0.4, 2.2]	24 (0.4) [0.2, 0.5]	17 (0.4)
Infections, n (IR), [95% CI]]						
Serious Infection	17 (4.2) [2.5, 6.8]	16 (3.8) [2.2, 6.2]	18 (3.3) [1.9, 5.2]	29 (4.8) [3.2, 6.9]	194 (2.9) [2.5, 3.4]	137 (3.2)
Herpes Zoster	4 (1.0) [0.3, 2.5]	18 (4.3)* [2.6, 6.8]	15 (2.7) [1.5, 4.5]	23 (3.8) [2.4, 5.7]	212 (3.2) [2.8, 3.7]	143 (3.4)
Tuberculosis	0	1 (0.2) [0.01,1.33]	0	6 (0.57) [0.21, 1.23]	10 (0.15) [0.07, 0.27]	7 (0.17)
MACE[c], n (IR), [95% CI]	2 (0.5) [0.1, 2.0]	3 (0.8) [0.2, 2.2]	1 (0.2) [0.0, 1.1]	2 (0.4) [0.05, 1.4]	31 (0.5) [0.4, 0.7]	16 (0.5)
GI Perforation, n (IR), [95% CI]	0	0	0	1 (0.20) [0.00, 0.92]	3 (0.05) [0.01, 0.13]	2 (0.05)

Genovese et Al., 2017

Reactivation of hepatitis B virus infection in patients with rheumatoid arthritis receiving tofacitinib: a real-world study

Yi-Ming Chen1,2,3,4, Wen-Nan Huang1,2, Yi-Da Wu1, Ching-Tsai Lin1, Yi-Hsing Chen1,2, Der-Yuan Chen1,2,3,4,5, Tsu-Yi Hsieh1,6

Tasso di incidenza di infezione da Herpes zoster per regione nei trial clinici con tofacitinib



- Incide
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- Cohen SB, et al. Ann Rheum Dis 2017;76:1253–1262.

Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis

K L Winthrop,[1] S-H Park,[2] A Gul,[3] M H Cardiel,[4] J J Gomez-Reino,[5] Y Tanaka,[6] K Kwok,[7] T Lukic,[7] E Mortensen,[8] D Ponce de Leon,[9] R Riese,[10] H Valdez[7]

Table 3 IRs of infections or malignancies, patients with events/100 patient-years (95% CI)

	All tofacitinib doses N=6194	Average tofacitinib 5 mg twice daily * N=2239	Average tofacitinib 10 mg twice daily * N=3955	Constant tofacitinib 5 mg twice daily † N=2342	Constant tofacitinib 10 mg twice daily † N=2814
Total patient-years of exposure, years	19 406	6870	12 536	3623	6702
Infections					
Serious infections (n=527)‡	2.7 (2.5 to 3.0)	3.1 (2.7 to 3.5)	2.6 (2.3 to 2.9)	2.3 (1.8 to 2.8)	2.7 (2.3 to 3.1)
HZ (non-serious and serious) (n=703)	3.9 (3.6 to 4.2)	3.8 (3.3 to 4.3)	4.0 (3.6 to 4.4)	3.5 (2.9 to 4.1)	4.1 (3.6 to 4.7)
HZ (serious‡) (n=53)	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.5)	0.2 (0.2 to 0.4)	0.3 (0.1 to 0.5)	0.2 (0.1 to 0.3)
Disseminated/ multidermatomal HZ (n=53)	0.3 (0.2 to 0.4)	NA	NA	0.1 (0.0 to 0.2)	0.2 (0.1 to 0.4)
Opportunistic infection, excluding TB (n=61)	0.3 (0.2 to 0.4)	0.4 (0.2 to 0.6)	0.3 (0.2 to 0.4)	0.2 (0.1 to 0.5)	0.3 (0.1 to 0.4)
Opportunistic infection, including TB (n=97)	0.5 (0.4 to 0.6)	0.5 (0.4 to 0.7)	0.5 (0.4 to 0.6)	0.3 (0.2 to 0.6)	0.5 (0.4 to 0.7)
TB (n=36)	0.2 (0.1 to 0.3)	0.1 (0.07 to 0.3)	0.2 (0.1 to 0.3)	0.08 (0.02 to 0.2)	0.3 (0.2 to 0.4)
Mortality due to infections (n=23)	0.1 (0.08 to 0.2)	0.2 (0.1 to 0.4)	0.1 (0.0 to 0.1)	0.2 (0.1 to 0.4)	0.05 (0.009 to 0.1)
Malignancies					
Malignancy excluding NMSC (n=173)	0.9 (0.8 to 1.0)	1.0 (0.8 to 1.3)	0.8 (0.7 to 1.0)	0.8 (0.5 to 1.2)	0.9 (0.7 to 1.2)
NMSC (n=118)	0.6 (0.5 to 0.7)	0.5 (0.4 to 0.7)	0.7 (0.5 to 0.8)	0.4 (0.3 to 0.7)	0.6 (0.5 to 0.9)
Lung (n=32)	0.2 (0.1 to 0.2)	0.2 (0.1 to 0.3)	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.4)	0.1 (0.1 to 0.2)
Breast (n=25)§	0.2 (0.1 to 0.2)	0.2 (0.1 to 0.3)	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.4)	0.2 (0.1 to 0.3)
Lymphoma (n=19)¶	0.1 (0.1 to 0.2)	0.09 (0.0 to 0.2)	0.1 (0.1 to 0.2)	0.1 (0.0 to 0.3)	0.1 (0.1 to 0.2)

Cohen, 2017

Agenda

- Safety Small molecules in AR e PsA
- Rischio infettivo
- **Rischio cardiovascolare**
- Rischio neoplastico
- Rischio/beneficio real world experience

Effects of Baricitinib on Lipid, Apolipoprotein, and Lipoprotein Particle Profiles in a Phase IIb Study of Patients With Active Rheumatoid Arthritis

Joel M. Kremer,[1] Mark C. Genovese,[2] Edward Keystone,[3] Peter C. Taylor,[4] Steven H. Zuckerman,[5] Giacomo Ruotolo,[5] Douglas E. Schlichting,[5] Victoria L. Crotzer,[5] Eric Nantz,[5] Scott D. Beattie,[5] and William L. Macias[5]

Table 3. Correlation analysis between lipid changes and changes in clinical end points from baseline to week 12*

Clinical end point	HDL cholesterol		LDL cholesterol		Triglycerides		Total cholesterol	
	r†	*P*	r†	*P*	r†	*P*	r†	*P*
DAS28-CRP	−0.23	<0.001	0.02	0.806	0.07	0.234	−0.03	0.572
DAS28-ESR	−0.17	0.004	0.09	0.143	0.07	0.273	0.05	0.419
SDAI	−0.14	0.022	0.00	0.980	0.12	0.059	0.00	0.984
CDAI	−0.08	0.185	0.01	0.921	0.13	0.031	0.03	0.590

* HDL = high-density lipoprotein; LDL = low-density lipoprotein; DAS28-CRP = Disease Activity Score 28-joint assessment using the C-reactive protein level; DAS28-ESR = DAS28 using the erythrocyte sedimentation rate; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index.
† Pearson partial correlation coefficient.

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Table 3. Correlation analysis between lipid changes and changes in clinical end points from baseline to week 12*

Clinical end point	HDL cholesterol		LDL cholesterol		Triglycerides		Total cholesterol	
	r†	*P*	r†	*P*	r†	*P*	r†	*P*
DAS28-CRP	−0.23	<0.001	0.02	0.806	0.07	0.234	−0.03	0.572
DAS28-ESR	−0.17	0.004	0.09	0.143	0.07	0.273	0.05	0.419
SDAI	−0.14	0.022	0.00	0.980	0.12	0.059	0.00	0.984
CDAI	−0.08	0.185	0.01	0.921	0.13	0.031	0.03	0.590

* HDL = high-density lipoprotein; LDL = low-density lipoprotein; DAS28-CRP = Disease Activity Score 28-joint assessment using the C-reactive protein level; DAS28-ESR = DAS28 using the erythrocyte sedimentation rate; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index.
† Pearson partial correlation coefficient.

Kremer, et Al. 2017

Table 3
Baseline demographics in Phase 3 and LTE studies

	Phase 3 studies						LTE studies		
	Tofacitinib 5 mg BID (N = 1589)	Tofacitinib 10 mg BID (N = 1611)	Placebo → tofacitinib 5 mg BID (N = 343)	Placebo → tofacitinib 10 mg BID (N = 338)	Adalimumab 40 mg sc q2w (N = 204)	Methotrexate (N = 186)	Tofacitinib 5 mg BID (N = 1452)	Tofacitinib 10 mg BID (N = 3374)	All doses (5 and 10 mg BID) (N = 4826)[a]
Age (years)									
Mean (range)	52.5 (18–86)	51.7 (18–85)	52.8 (18–82)	52.2 (18–80)	52.5 (23–77)	48.8 (20–80)	53.1 (18–82)	53.0 (18–86)	53.1 (18–86)
≥65 years (%)	14.3	14.3	16.3	13.3	14.7	10.8	17.1	15.4	15.9
Gender (%)									
Male: female	17.4: 82.6	15.8: 84.2	19.0: 81.0	18.6: 81.4	20.6: 79.4	22.0: 78.0	16.8: 83.2	18.1: 81.9	17.7: 82.3
Race (%)									
White	61.4	62.5	66.8	62.1	72.5	68.3	46.6	70.5 3.2 16.3 10.0	63.3
Black	3.7	2.9	2.3	4.7	1.5	2.2	1.7	3.2	2.7
Asian	24.9	23.4	23.6	25.1	14.2	17.7	43.1	16.3	24.4
Other	10.1	11.2	7.3	8.0	11.8	11.8	8.7	10.0	9.6
Smoker (%)									
Never: current: ex-smoker	66.6: 14.7: 18.7	68.1: 17.5: 14.4	59.2: 21.1: 19.6	66.4: 17.0: 16.7	65.5: 18.5: 16.0	67.2: 21.0: 11.8	73.6: 13.3: 13.1	65.7: 18.1: 16.2	67.9: 16.8: 15.3
Mean (SD) body mass index (kg/m^2)	26.9 (6.5)	27.0 (6.3)	26.8 (6.6)	27.6 (7.1)	27.1 (5.5)	26.7 (6.1)	25.5 (5.8)	27.5 (6.5)	26.9 (6.4)

	Tofacitinib 5 mg BID (N = 1589)	Tofacitinib 10 mg BID (N = 1611)	All tofacitinib doses (N = 3200)	Placebo (N = 681)	Adalimumab 40 mg sc q2w (N = 204)	Methotrexate (N = 186)	Tofacitinib 5 mg BID (N = 1452)	Tofacitinib 10 mg BID (N = 3374)	All doses (5 and 10 mg BID) (N = 4827)
Hypertension, n (%)	369 (23.2)	358 (22.2)	727 (22.7)	145 (21.3)	49 (24.0)	33 (17.7)	365 (25.5)	735 (22.1)	1100 (23.1)
Diabetes, n (%)	130 (8.2)	127 (7.9)	257 (8.0)	48 (7.0)	16 (7.8)	8 (4.3)	107 (7.4)	243 (7.2)	350 (7.3)
Mean (SD) LDL-C (mg/dL)	114.8 (34.2)	113.3 (34.9)	114.1 (34.5)	115.8 (35.0)	117.0 (34.3)	111.5 (32.0)	111.5 (32.6)	114.2 (34.4)	113.4 (33.9)
Mean (SD) HDL-C (mg/dL)	59.4 (16.9)	59.7 (17.0)	59.6 (16.9)	59.8 (17.1)	58.6 (16.5)	55.7 (15.0)	58.7 (16.3)	59.0 (16.5)	58.9 (16.5)
Mean (SD) TC (mg/dL)	199.1 (42.4)	198.6 (42.8)	198.8 (42.6)	200.6 (41.7)	200.8 (40.3)	190.1 (39.7)	192.1 (39.6)	198.8 (41.7)	196.6 (41.2)
Mean (SD) Triglycerides (mg/dL)	124.6 (68.7)	128.6 (78.8)	126.6 (74.0)	125.2 (64.3)	126.1 (60.2)	115.2 (51.2)	113.3 (63.1)	125.5 (70.2)	121.8 (63.4)

In Phase 3 studies, patients randomized to placebo were advanced in a blinded manner to tofacitinib 5 or 10 mg BID at Months 3 or 6.
The average total daily dose (TDD) during the LTE studies was calculated by adding all doses received by each patient and dividing by the number of days a dose was received. TDDs of < 15 mg/day and ≥ 15 mg/day were categorized as 5 and 10 mg BID groups, respectively.
BID, twice daily; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LTE, long-term extension; q2w, once every 2 weeks; sc, subcutaneously; SD, standard deviation; TC, total cholesterol.
[a] One subject had no demographic data at the time of the analysis.

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Hypertension-related adverse events in Phase 3 studies (A) and LTE studies (B)

(A)

	Tofacitinib 5 mg BID $N = 1589$	Tofacitinib 10 mg BID $N = 1611$	All tofacitinib doses $N = 3200$	Placebo $N = 681$	Adalimumab 40 mg sc q2w $N = 204$	Methotrexate $N = 186$
Up to Month 3, *n* (%)						
Blood pressure diastolic increased	0	1 (0.1)	1 (0.03)	0	0	0
Blood pressure increased	7 (0.4)	6 (0.4)	13 (0.4)	3 (0.4)	0	0
Blood pressure systolic increased	0	1 (0.1)	1 (0.03)	0	0	0
Hypertension	27 (1.7)	43 (2.7)	70 (2.2)	7 (1.0)	0	2 (1.1)
Hypertensive crisis	1 (0.1)	3 (0.2)	4 (0.1)	0	0	0
Total	**35 (2.2)**	**54 (3.4)**	**89 (2.8)**	**10 (1.5)**	**0**	**2 (1.1)**
	$N = 1824$	$N = 1836$	$N = 3660$	$N = 221$	$N = 204$	$N = 186$
Months 3–6, *n* (%)						
Retinopathy hypertensive	1 (0.1)	0	1 (0.03)	0	0	0
Blood pressure diastolic increased	0	0	0	1 (0.5)	0	0
Blood pressure increased	2 (0.1)	3 (0.2)	5 (0.1)	0	0	0
Blood pressure systolic increased	0	1 (0.1)	1 (0.03)	0	0	0
Hypertension	22 (1.2)	22 (1.2)	44 (1.2)	1 (0.5)	0	0
Hypertensive crisis	1 (0.1)	0	1 (0.03)	0	0	0
Total	**26 (1.4)**	**26 (1.4)**	**52 (1.4)**	**2 (0.9)**	**0**	**0**
	$N = 1429$	$N = 1443$	$N = 2872$	–	$N = 204$	$N = 186$

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> 6 Months, *n* (%)						
Hypertensive cardiomyopathy	0	1 (0.1)	1 (0.03)	–	0	0
Blood pressure increased	6 (0.4)	4 (0.3)	10 (0.3)	–	0	1 (0.5)
Blood pressure systolic increased	1 (0.1)	0	1 (0.03)	–	0	0
Essential hypertension	0	0	0	–	1 (0.5)	0
Hypertension	38 (2.7)	29 (2.0)	67 (2.3)	–	2 (1.0)	1 (0.5)
Hypertensive crisis	1 (0.1)	1 (0.1)	2 (0.1)	–	0	0
Total	**45 (3.1)**	**34 (2.1)**	**79 (2.8)**	**–**	**3 (1.5)**	**2 (1.1)**

(B)

n (%)	Tofacitinib 5 mg BID *N* = 1452	Tofacitinib 10 mg BID *N* = 3375	All doses (5 and 10 mg BID) *N* = 4827
Retinopathy hypertensive	0	1 (0.03)	1 (0.02)
Blood pressure abnormal	0	1 (0.03)	1 (0.02)
Blood pressure diastolic increased	0	3 (0.1)	3 (0.1)
Blood pressure increased	22 (1.5)	34 (1.0)	56 (1.2)
Metabolic syndrome	0	2 (0.1)	2 (0.04)
Hypertensive encephalopathy	1 (0.1)	0	1 (0.02)
Accelerated hypertension	1 (0.1)	1 (0.03)	2 (0.04)
Blood pressure inadequately controlled	0	1 (0.03)	1 (0.02)
Essential hypertension	0	1 (0.03)	1 (0.02)
Hypertension	140 (9.6)	168 (5.0)	308 (6.4)
Hypertensive crisis	5 (0.3)	10 (0.3)	15 (0.3)
Systolic hypertension	0	2 (0.1)	2 (0.04)
Total	**169 (11.6)**	**224 (6.6)**	**393 (8.1)**

In Phase 3 studies, patients randomized to placebo were advanced in a blinded manner to tofacitinib 5 or 10 mg BID at Months 3 or 6. The "All tofacitinib doses" group includes placebo patients who advanced to tofacitinib where applicable.
The average total daily dose (TDD) during the LTE studies was calculated by adding all doses received by each patient and dividing by the number of days a dose was received. TDDs of < 15 mg/day and ≥ 15 mg/day were categorized as 5 and 10 mg BID groups, respectively.
BID, twice daily; LTE, long-term extension; q2w, once every 2 weeks; sc, subcutaneously.

Schoeman et al, 2016

Table 3
Baseline demographics in Phase 3 and LTE studies

	Phase 3 studies						LTE studies		
	Tofacitinib 5 mg BID (N = 1589)	Tofacitinib 10 mg BID (N = 1611)	Placebo → tofacitinib 5 mg BID (N = 343)	Placebo → tofacitinib 10 mg BID (N = 338)	Adalimumab 40 mg sc q2w (N = 204)	Methotrexate (N = 186)	Tofacitinib 5 mg BID (N = 1452)	Tofacitinib 10 mg BID (N = 3374)	All doses (5 and 10 mg BID) (N = 4826)[a]
Age (years)									
Mean (range)	52.5 (18–86)	51.7 (18–85)	52.8 (18–82)	52.2 (18–80)	52.5 (23–77)	48.8 (20–80)	53.1 (18–82)	53.0 (18–86)	53.1 (18–86)
≥65 years (%)	14.3	14.3	16.3	13.3	14.7	10.8	17.1	15.4	15.9
Gender (%)									
Male: female	17.4: 82.6	15.8: 84.2	19.0: 81.0	18.6: 81.4	20.6: 79.4	22.0: 78.0	16.8: 83.2	18.1: 81.9	17.7: 82.3
Race (%)									
White	61.4	62.5	66.8	62.1	72.5	68.3	46.6	70.5 3.2 16.3 10.0	63.3
Black	3.7	2.9	2.3	4.7	1.5	2.2	1.7	3.2	2.7
Asian	24.9	23.4	23.6	25.1	14.2	17.7	43.1	16.3	24.4
Other	10.1	11.2	7.3	8.0	11.8	11.8	8.7	10.0	9.6
Smoker (%)									
Never: current: ex-smoker	66.6: 14.7: 18.7	68.1: 17.5: 14.4	59.2: 21.1: 19.6	66.4: 17.0: 16.7	65.5: 18.5: 16.0	67.2: 21.0: 11.8	73.6: 13.3: 13.1	65.7: 18.1: 16.2	67.9: 16.8: 15.3
Mean (SD) body mass index (kg/m^2)	26.9 (6.5)	27.0 (6.3)	26.8 (6.6)	27.6 (7.1)	27.1 (5.5)	26.7 (6.1)	25.5 (5.8)	27.5 (6.5)	26.9 (6.4)

	Tofacitinib 5 mg BID (N = 1589)	Tofacitinib 10 mg BID (N = 1611)	All tofacitinib doses (N = 3200)	Placebo (N = 681)	Adalimumab 40 mg sc q2w (N = 204)	Methotrexate (N = 186)	Tofacitinib 5 mg BID (N = 1452)	Tofacitinib 10 mg BID (N = 3374)	All doses (5 and 10 mg BID) (N = 4827)
Hypertension, n (%)	369 (23.2)	358 (22.2)	727 (22.7)	145 (21.3)	49 (24.0)	33 (17.7)	365 (25.5)	735 (22.1)	1100 (23.1)
Diabetes, n (%)	130 (8.2)	127 (7.9)	257 (8.0)	48 (7.0)	16 (7.8)	8 (4.3)	107 (7.4)	243 (7.2)	350 (7.3)
Mean (SD) LDL-C (mg/dL)	114.8 (34.2)	113.3 (34.9)	114.1 (34.5)	115.8 (35.0)	117.0 (34.3)	111.5 (32.0)	111.5 (32.6)	114.2 (34.4)	113.4 (33.9)
Mean (SD) HDL-C (mg/dL)	59.4 (16.9)	59.7 (17.0)	59.6 (16.9)	59.8 (17.1)	58.6 (16.5)	55.7 (15.0)	58.7 (16.3)	59.0 (16.5)	58.9 (16.5)
Mean (SD) TC (mg/dL)	199.1 (42.4)	198.6 (42.8)	198.8 (42.6)	200.6 (41.7)	200.8 (40.3)	190.1 (39.7)	192.1 (39.6)	198.8 (41.7)	196.6 (41.2)
Mean (SD) Triglycerides (mg/dL)	124.6 (68.7)	128.6 (78.8)	126.6 (74.0)	125.2 (64.3)	126.1 (60.2)	115.2 (51.2)	113.3 (63.1)	125.5 (70.2)	121.8 (63.4)

In Phase 3 studies, patients randomized to placebo were advanced in a blinded manner to tofacitinib 5 or 10 mg BID at Months 3 or 6.
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BID, twice daily; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LTE, long-term extension; q2w, once every 2 weeks; sc, subcutaneously; SD, standard deviation; TC, total cholesterol.
[a] One subject had no demographic data at the time of the analysis.

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While further studies are in progress, the analysis of the data presented in the current work does not suggest an increase in CV events associated with these lipid changes.

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Agenda

- Safety Small molecules in AR e PsA
- Rischio infettivo
- Rischio cardiovascolare
- **Rischio neoplastico**
- Rischio/beneficio real world experiece

Table 3 IRs of infections or malignancies, patients with events/100 patient-years (95% CI)

	All tofacitinib doses N=6194	Average tofacitinib 5 mg twice daily * N=2239	Average tofacitinib 10 mg twice daily * N=3955	Constant tofacitinib 5 mg twice daily † N=2342	Constant tofacitinib 10 mg twice daily † N=2814
Total patient-years of exposure, years	19 406	6870	12 536	3623	6702
Infections					
Serious infections (n=527)‡	2.7 (2.5 to 3.0)	3.1 (2.7 to 3.5)	2.6 (2.3 to 2.9)	2.3 (1.8 to 2.8)	2.7 (2.3 to 3.1)
HZ (non-serious and serious) (n=703)	3.9 (3.6 to 4.2)	3.8 (3.3 to 4.3)	4.0 (3.6 to 4.4)	3.5 (2.9 to 4.1)	4.1 (3.6 to 4.7)
HZ (serious‡) (n=53)	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.5)	0.2 (0.2 to 0.4)	0.3 (0.1 to 0.5)	0.2 (0.1 to 0.3)
Disseminated/ multidermatomal HZ (n=53)	0.3 (0.2 to 0.4)	NA	NA	0.1 (0.0 to 0.2)	0.2 (0.1 to 0.4)
Opportunistic infection, excluding TB (n=61)	0.3 (0.2 to 0.4)	0.4 (0.2 to 0.6)	0.3 (0.2 to 0.4)	0.2 (0.1 to 0.5)	0.3 (0.1 to 0.4)
Opportunistic infection, including TB (n=97)	0.5 (0.4 to 0.6)	0.5 (0.4 to 0.7)	0.5 (0.4 to 0.6)	0.3 (0.2 to 0.6)	0.5 (0.4 to 0.7)
TB (n=36)	0.2 (0.1 to 0.3)	0.1 (0.07 to 0.3)	0.2 (0.1 to 0.3)	0.08 (0.02 to 0.2)	0.3 (0.2 to 0.4)
Mortality due to infections (n=23)	0.1 (0.08 to 0.2)	0.2 (0.1 to 0.4)	0.1 (0.0 to 0.1)	0.2 (0.1 to 0.4)	0.05 (0.009 to 0.1)
Malignancies					
Malignancy excluding NMSC (n=173)	0.9 (0.8 to 1.0)	1.0 (0.8 to 1.3)	0.8 (0.7 to 1.0)	0.8 (0.5 to 1.2)	0.9 (0.7 to 1.2)
NMSC (n=118)	0.6 (0.5 to 0.7)	0.5 (0.4 to 0.7)	0.7 (0.5 to 0.8)	0.4 (0.3 to 0.7)	0.6 (0.5 to 0.9)
Lung (n=32)	0.2 (0.1 to 0.2)	0.2 (0.1 to 0.3)	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.4)	0.1 (0.1 to 0.2)
Breast (n=25)§	0.2 (0.1 to 0.2)	0.2 (0.1 to 0.3)	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.4)	0.2 (0.1 to 0.3)
Lymphoma (n=19)¶	0.1 (0.1 to 0.2)	0.09 (0.0 to 0.2)	0.1 (0.1 to 0.2)	0.1 (0.0 to 0.3)	0.1 (0.1 to 0.2)

Cohen, 2017

Table 1. Safety outcomes with up to 5.5 years of exposure to baricitinib

	PBO-bari 4 mg[a] (6 study, to Week 24)		Bari 2 mg-4 mg-extended[b] (4 study, including LTE)		All-bari-RA 01-Sept-2016	All-bari-RA 10-Aug-2015
	PBO	Bari 4 mg	Bari 2 mg	Bari 4 mg	All Bari RA	All Bari RA
Exposure						
Number of patients	1070	997	479	479	3492	3464
Patient-years of exposure	393.8	409.4	554.5	604	6637	4214
Median, days	166	169	257.0	342	760 (2.1 yrs)	--
Longest exposure, days	235	211	1276	1991	2019 (5.5 yrs)	--
Permanent DC due to AE, n (EAIR)	35 (8.9)	47 (11.5)	37 (6.6)	55 (8.9)	393 (5.8)	255 (6.1)
Mortality, n (IR), [95% CI]	2 (0.5) [0.1, 1.8]	3 (0.7) [0.1, 2.1]	1 (0.18) [0.00, 1.0]	3 (0.49) [0.1, 1.4]	22 (0.33) [0.2, 0.5]	13 (0.3)
Malignancy, n (IR), [95% CI]						
Malignancy excluding NMSC	2 (0.5) [0.1, 1.8]	2 (0.5) [0.1, 1.7]	3 (0.5) [0.1, 1.6]	8 (1.3) [0.6, 2.6]	52 (0.8) [0.6, 1.0]	29 (0.7)
	--	--	7 (0.7)[RAN] [0.3, 1.4]	9 (0.9)[RAN] [0.4, 1.6]	--	--
Lymphoma	0	0	0	1 (0.09) [0.002, 0.52]	6 (0.09) [0.03, 0.19]	3 (0.07)
NMSC	1 (0.2) [0.0, 1.4]	3 (0.7) [0.1, 2.1]	2 (0.4) [0.04, 1.3]	6 (1.0) [0.4, 2.2]	24 (0.4) [0.2, 0.5]	17 (0.4)
Infections, n (IR), [95% CI]]						
Serious Infection	17 (4.2) [2.5, 6.8]	16 (3.8) [2.2, 6.2]	18 (3.3) [1.9, 5.2]	29 (4.8) [3.2, 6.9]	194 (2.9) [2.5, 3.4]	137 (3.2)
Herpes Zoster	4 (1.0) [0.3, 2.5]	18 (4.3)* [2.6, 6.8]	15 (2.7) [1.5, 4.5]	23 (3.8) [2.4, 5.7]	212 (3.2) [2.8, 3.7]	143 (3.4)
Tuberculosis	0	1 (0.2) [0.01,1.33]	0	6 (0.57) [0.21, 1.23]	10 (0.15) [0.07, 0.27]	7 (0.17)
MACE[c], n (IR), [95% CI]	2 (0.5) [0.1, 2.0]	3 (0.8) [0.2, 2.2]	1 (0.2) [0.0, 1.1]	2 (0.4) [0.05, 1.4]	31 (0.5) [0.4, 0.7]	16 (0.5)
GI Perforation, n (IR), [95% CI]	0	0	0	1 (0.20) [0.00, 0.92]	3 (0.05) [0.01, 0.13]	2 (0.05)

Genovese et Al., 2017

Agenda

- Safety Small molecules in AR e PsA
- Rischio infettivo
- Rischio cardiovascolare
- Rischio neoplastico
- **Rischio/beneficio real world experience**

Table 1
Clinically relevant medication interactions with tofacitinib

CYP Subset	Inhibitors	Inducers
CYP3A4	Clarithromycin Erythromycin Ketoconazole Itraconazole Diltiazem Verapamil Nelfinavir Ritonavir	Rifampin Phenytoin Carbamazepine
CYP2C19	Fluoxetine Fluvoxamine Isoniazid Ritonavir	Rifampicin Phenytoin Carbamazepine

Betancourt et Al, 2018

Therapeutics and Clinical Risk Management

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REVIEW

European perspective on the management of rheumatoid arthritis: clinical utility of tofacitinib

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Tomasz Brzostek[3]
Maria Kózka[4]

Clinical laboratory results during tofacitinib treatment in RA

Parameter	Observation period		
	0–3 months	3–24 months	>24 months (LTE studies)
Neutrophil count	Decrease[53]	Slow decrease[53]	Stabilization[53]
Lymphocyte count	Increase[53]	Slow decrease[53]	Stabilization[53]
Hemoglobin level	Increase[53]	Slow increase up to 12 months; then stabilization[53]	No clear tendency[53]
LDL level	Increase[24,30,32,33]	Increase or stabilization[24,29,30,35]	Stabilization[38]
HDL level	Increase[32,33]	Increase or stabilization[29,35]	No data available
Serum creatine level	Increase[24,32]	Slow increase[24,34,35]	Stabilization[38]

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; LTE, long-term extension studies; RA, rheumatoid arthritis.

- Kawalec P et al. Therapeutics and Clinical Risk Management 2018:14 15–29

Box 5
Clinical pearls: tofacitinib

- Tofacitinib is a new and effective treatment option for RA, which could be used with or without MTX.
- Patients should receive screening for tuberculosis before therapy initiation.
- Risk of infections including herpes zoster may be higher in patients receiving tofacitinib, specifically Asian patients.
- Tofacitinib therapy may blunt the immune response to specific vaccines; therefore, patients should be assessed for appropriate immunizations against herpes zoster, influenza, and pneumococcus before commencing therapy.

Betancourt et Al, 2018

Box 6
Clinical pearls: apremilast

- Apremilast has a favorable safety profile and is likely a viable therapeutic option for elderly patients with psoriatic arthritis.
- Evaluate risks of depression and monitor weight during therapy.
- Routine laboratory monitoring is not required during apremilast therapy.

Betancourt et Al, 2018

RHEUMATOLOGY

Review

doi:10.1093/rheumatology/key165

Management of inflammatory rheumatic conditions in the elderly

Clément Lahaye[1], Zuzana Tatar[1], Jean-Jacques Dubost[1], Anne Tournadre[1] and Martin Soubrier[1]

Rheumatology key messages

- Elderly inflammatory rheumatic disease patients should be provided with individualized care.
- A multimodal evaluation could improve the quality of care for elderly IRD patients.
- Studies of elderly care are necessary to develop specific recommendations in IRD.

Lahaye et Al., 2018

Pharmacotherapy Pearls in Rheumatology for the Care of Older Adult Patients

Focus on Oral Disease-Modifying Antirheumatic Drugs and the Newest Small Molecule Inhibitors

Blas Y. Betancourt, MD[a,*], Ann Biehl, MS, PharmD, BCPS[b], James D. Katz, MD[a], Ananta Subedi, MD[a]

KEY POINTS

- Older patients with rheumatic disorders are at increased risk for therapeutic misadventure because of age-related pharmacokinetic and pharmacodynamic changes, polypharmacy, comorbidities, impaired health literacy secondary to decreased cognition, and provider age bias.
- Rheumatologists along with other members of the allied health care team can most effectively minimize the risk for medication-related adverse reactions in older patients.
- Familiarity with dosing, monitoring, adverse reactions, medication interactions, and amelioration strategies can improve the safety of disease-modifying antirheumatic drugs in the older rheumatology patient.

Betancourt et Al., 2018

Ringraziamenti

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