Supplementary information for the manuscript:

The impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis

Contents

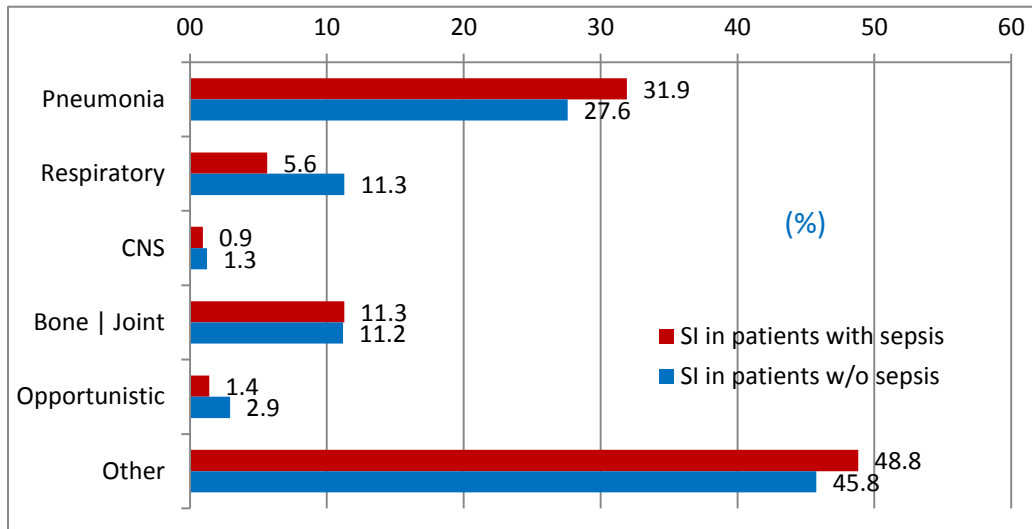## Figure S1: Spectrum of SI stratified by the development of sepsis.

Figure S2: In RABBIT a total of 1,017 serious infections (SI) have been reported until October, 30th in 2013.

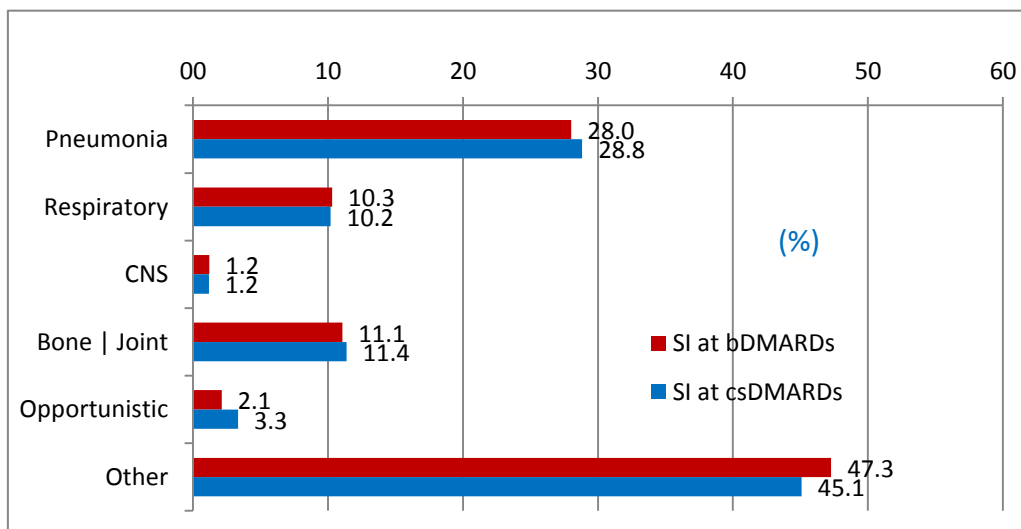## Figure S2: Spectrum of SI stratified by DMARD groups.

Table S1: Univariate associations regarding risks of sepsis and death.

	OR Sepsis	95% CI	OR Death	95% CI
Age (by 10 years)	1.52	[1.26, 1.83]	2.73	[1.90, 3.94]
Sex (males vs females)	1.03	[0.69, 1.54]	1.50	[0.84, 2.68]
Physical function (by 10% improvement)	0.88	[0.82, 0.94]	0.80	[0.72, 0.90]
ESR	1.04	[1.01, 1.08]	1.04	[0.99, 1.10]
CRP	1.01	[1.00, 1.01]	1.00	[0.99, 1.01]
DAS28 (<3.2)				
DAS28 (3.2 - 5.1)	1.50	[0.90, 2.51]	1.23	[0.58, 2.62]
DAS28 (>5.1)	1.58	[0.92, 2.71]	1.31	[0.59, 2.89]
GC (<5 mg/d=Reference)				
GC (5- <10mg/d vs. Ref.)	1.42	[0.93, 2.15]	1.15	[0.60, 2.21]
GC (≥10mg/d vs. Ref.)	1.66	[0.97, 2.83]	2.23	[1.06, 4.71]
TNFi (yes vs no)	0.71	[0.48, 1.04]	0.55	[0.30, 1.02]
Other bDMARD (yes vs. no)	0.61	[0.36, 1.05]	0.26	[0.08, 0.84]
Heart failure (yes vs. no)	2.16	[1.27, 3.68]	6.67	[3.59, 12.38]
Diabetes (yes vs. no)	1.65	[1.08, 2.53]	1.90	[1.02, 3.55]
Coronary heart disease (yes vs. no)	1.89	[1.19, 3.01]	3.18	[1.71, 5.94]
COPD (yes vs. no)	0.98	[0.60, 1.59]	1.74	[0.92, 3.30]
Hypertension (yes vs. no)	1.57	[1.07, 2.30]	1.84	[1.01, 3.36]
Chronic renal disease (yes vs. no)	2.34	[1.43, 3.82]	2.32	[1.12, 4.81]
Cerebrovascular disease	2.11	[0.87, 5.08]	3.19	[1.05, 9.70]

Abbreviations: ESR=erythrocyte sedimentation rate, CRP=c-reactive protein, DAS28=disease activity score (28 joint count), GC=glucocorticoids, TNFi=tumor necrosis factor-α inhibitor (adalimumab, etanercept, infliximab, golimumab, certolizumab), OR=odds ratio, CI=confidence interval, COPD=chronic obstructive pulmonary disease, other bDMARD=other biologic disease modifying anti-rheumatic drugs (tocilizumab, rituximab, abatacept).

Table S2: Patient characteristics stratified by the class of DMARD exposure at pneumonia.

	TNFi	Other bDMARDs	csDMARDs
N	116	49	133
Age at SI (mean (sd), years)	61.9 (12.4)	62.8 (11.2)	66.1 (11.5)
Sex (female, n (%))	84 (72.4)	28 (57.1)	77 (57.9)
RF positive (n (%))	98 (84.5)	36 (73.5)	110 (82.7)
Disease duration at SI (mean (sd), years)	14.2 (9)	15.0 (9.1)	14.2 (11.5)
Previous bDMARD exposure	116 (100)	49 (100)	75 (56.4)
CRP (mean (sd))	24.2 (39.7)	23.7 (37.4)	22.4 (27.7)
DAS28 (mean (sd))	4.5 (1.4)	4.4 (1.6)	4.4 (1.4)
% of physical function (sd)	54.5 (24.1)	52.3 (24.8)	53.4 (26.0)
Selected comorbidities:			
Heart failure	14 (12.1)	9 (18.4)	20 (15.0)
Chronic renal disease	19 (16.4)	10 (20.4)	28 (21.1)
Events of interest			
Death (≤90d) w/o Sepsis	7 (6.0)	1 (2.0)	21 (15.8)
Sepsis (≤30d, n)	18 (15.5)	10 (20.4)	36 (27.1)
Overall death after Sepsis	10 (55.6)	6 (60.0)	31 (86.1)

Abbreviations: N=number, SI=serious infection, RF=rheumatoid factor, CRP=c-reactive protein, DAS28=disease activity score 28-joint count, sd=standard deviation, w/o=without.

Table S3: Results of multinomial regression - sepsis and death after pneumonia.

	OR Sepsis	95% CI	OR Death	95% CI
Age (by 10 years)	1.57	[1.15; 2.13]	2.01	[1.18; 3.44]
Sex (males vs females)	0.63	[0.33; 1.23]	1.12	[0.44; 2.86]
FFbH (by 10% improvement)	0.93	[0.82; 1.06]	0.84	[0.70; 1.01]
GC (<5 mg/d=Reference)				
GC (5- <10mg/d vs. Ref.)	1.91	[0.96; 3.81]	1.18	[0.39; 3.53]
GC (≥10mg/d vs. Ref.)	1.24	[0.44; 3.48]	4.39	[1.24; 15.46]
TNFi (vs. csDMARD)	0.44	[0.22; 0.87]	0.30	[0.11; 0.83]
Other bDMARD (vs. csDMARD)	0.56	[0.24; 1.32]	0.06	[0.01; 0.56]
Heart failure (yes vs. no)	1.32	[0.55; 3.21]	5.58	[2.01; 15.48]
Chronic renal disease (yes vs. no)	1.30	[0.62; 2.74]	0.92	[0.31; 2.71]

The adjusted odds ratios specify increase or decrease in the risk of developing the outcome (sepsis or death) compared to patients in whom the SI could be healed (reference group). Abbreviations: GC=glucocorticoids, TNFi=tumor necrosis factor-α inhibitor (adalimumab, etanercept, infliximab, golimumab, certolizumab), OR=odds ratio, CI=confidence interval, other bDMARD=other biologic disease modifying anti-rheumatic drugs (tocilizumab, rituximab, abatacept).

Table S4: Patient characteristics according to bDMARD exposure at 1st SI

At time of SI:	bDMARD naive	bDMARD exposed	bDMARD discontinued
N	134	517	212
Age at SI (mean (sd), years)	65.5 (11.1)	60.9 (11.6)	63 (11.6)
Sex (female, n (%))	93 (69.4)	377 (72.9)	157 (74.1)
RF positive (n (%))	99 (73.9)	424 (82.0)	166 (78.3)
Disease duration at SI (mean (sd), years)	9.3 (8.5)	14.8 (10.1)	17.1 (11.5)
DAS28 (mean (sd))	4.1 (1.4)	4.4 (1.5)	4.5 (1.4)
CRP (mean (sd))	16.7 (19.6)	18.2 (28.5)	19.8 (30)
% of physical function (sd)	64.9 (23.7)	55.0 (25.1)	50.3 (25.2)
GC (<5 mg/d=Reference)	49 (36.6)	190 (36.8)	73 (34.4)
GC (5- <10mg/d vs. Ref.)	67 (50.0)	239 (46.2)	104 (49.1)
GC (≥10mg/d vs. Ref.)	18 (13.4)	88 (17.0)	35 (16.5)
Selected comorbidities:			
Heart failure	10 (7.5)	55 (10.6)	21 (9.9)
Chronic renal disease	14 (10.4)	64 (12.4)	34 (16.0)

Table S5: Results of multinomial regression regarding the impact of bDMARD discontinuation

	OR: Sepsis	95% CI	OR: Death	95% CI
Age at SI (by 10 years)	1.41	[1.16; 1.72]	2.42	[1.62; 3.60]
Sex (males vs. females)	1.00	[0.65; 1.54]	1.44	[0.75; 2.76]
Physical function (by 10% improvement)	0.91	[0.84; 0.99]	0.86	[0.76; 0.98]
GC (<5 mg/d)	Ref.	.	Ref.	.
GC (5- <10mg/d)	1.28	[0.83; 1.96]	0.94	[0.47; 1.87]
GC (≥10mg/d)	1.65	[0.94; 2.91]	2.42	[1.06; 5.52]
bDMARD naive	Ref.	.	Ref.	.
bDMARD current exposure	0.57	[0.34; 0.97]	0.34	[0.15; 0.80]
bDMARD discontinued	0.97	[0.56; 1.70]	0.96	[0.42; 2.17]
Heart failure (yes vs. no)	1.35	[0.76; 2.39]	3.41	[1.70; 6.82]
Renal disease (yes vs. no)	1.93	[1.20; 3.09]	1.51	[0.74; 3.08]

Results of multiple multinomial regression for the events of sepsis and death after 1st SI in patients exposed (never vs. current vs. previous) to bDMARDs. Abbreviations: SI=serious infection, OR=odds ratio, CI=confidence interval.

Table S6: Odds ratios for mortality after sepsis in patients with pneumonia.

	Death from sepsis after pneumonia	
	OR	95% CI
Age (by 10 years)	1.77	[0.91; 3.45]
Sex (males vs females)	1.47	[0.28; 7.85]
FFbH (by 10% improvement)*		
GC (<5 mg/d=Reference)*		
GC (5- <10mg/d vs. Ref.)*		
GC (≥10mg/d vs. Ref.)*		
TNFi (yes vs. no)	0.18	[0.05; 0.91]
Other bDMARD (yes vs. no)	0.25	[0.06; 1.54]
Heart failure (yes)	2.35	[0.37;14.87]
Chronic renal disease (yes)*		

Results of multiple logistic regression for the risk of death after sepsis in patients with pneumonia. Abbreviations: OR=odds ratio, CI=confidence interval, GC=glucocorticoids, TNFi=tumor necrosis factor-α inhibitor.*=these covariates were omitted in the adjustment due to the small number of patients and events and for the purpose of model sparsity.