

Biologic DMARDs and targeted synthetic DMARDs and the risk of all-cause mortality in rheumatoid arthritis

A systematic review and meta-analysis

Mengduan Pang, MD^a, Zhe Sun, MD^b, Hongfeng Zhang, PhD^a

Abstract

Background: The aim of this study was to perform a meta-analysis to compare the risk of all-cause mortality between biological/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) and non-b/tsDMARDs involving patients with rheumatoid arthritis (RA).

Methods: We performed a systematic review of articles published up to August 2021 using electronic databases. We included studies that reported all-cause mortality in RA patients and compared b/tsDMARDs and non-b/tsDMARDs.

Results: We included a total of 77 studies involving 64,428 patients. These comprised 44,227 patients treated with b/tsDMARDs and 20,201 treated with non-b/tsDMARDs. The occurrence of all-cause mortality was the primary outcome. The risk of all-cause mortality between the 2 treatments was not significantly different (relative risk = 1.08; 95% confidence interval = 0.98-1.19). However, subgroup analyses showed significant increase in risks of mortality in anti-TNFs users with RA compared with non-b/tsDMARDs (relative risk = 1.47, 95% confidence interval = 1.02-2.12). No significant differences were found after subgroup analyses based on other molecules involved and study duration.

Conclusion: In comparison with non-b/tsDMARDs, our results suggest that antitumor necrosis factor therapy is associated with observed increased risks of mortality and further investigation is needed.

Abbreviations: ACR = American College of Rheumatology, anti-CD20 = anti-cluster of differentiation 20, b/tsDMARDs = biological/ targeted synthetic disease-modifying antirheumatic drugs, CI = confidence interval, CTLA4Ig = cytotoxic T lymphocyte antigen-4 lg, EULAR = European League Against Rheumatism, ilL-6 = interleukin-6 inhibitor, iJAK = janus kinase inhibitor, RA = rheumatoid arthritis, RR = relative risk.

Keywords: DMARDs, mortality, rheumatoid arthritis

1. Introduction

During the past 2 decades, biological disease-modifying antirheumatic drugs (bDMARDs)^[1] and targeted synthetic (ts) DMARDs^[2] have been demonstrated to be effective in the treatment of rheumatoid arthritis (RA). These drugs have played a significant role in improving the clinical symptoms and enhancing the quality of life of patients^[3,4] and were recommended by the European League Against Rheumatism (EULAR).^[5] At present, bDMARDs and tsDMARDs are widely used.

However, it is still unclear whether bDMARDs or tsD-MARDs^[6] can improve the mortality rate in patients with RA. Since inflammatory factors play a significant role in antitumor and anti-infection responses, much has been written about the concern that these new drugs may increase the risks of infections,^[7,8] malignancy,^[9,10] heart disease,^[11] and other serious

adverse events. Data from the British Society for Rheumatology Biologics Register showed that the proportion of deaths attributable to RA-interstitial lung disease is higher in patients treated with anti-tumor necrosis factor (TNF) therapy.^[12] On the other hand, RA can be well controlled using b/tsDMARDs. Owing to chronic inflammation could be well controlled and the rate of glucocorticoid use was reduced, these therapeutics appear superior to conventional synthetic (cs) DMARDs in reducing mortality.^[13–15] But no difference was also found in the risk of mortality between b/tsDMARDs and csDMARDs, as mentioned in some other research works.^[16,17]

In order to reveal the association between the use of b/tsD-MARDs and the risks of mortality events in RA patients further, we designed and performed a meta-analysis with the aim to evaluate whether treatments with b/tsDMARDs would reduce the risk of mortality events in patients with RA.

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All data relevant to the study are included in the article. No more additional data are available.

The authors have no competing interest.

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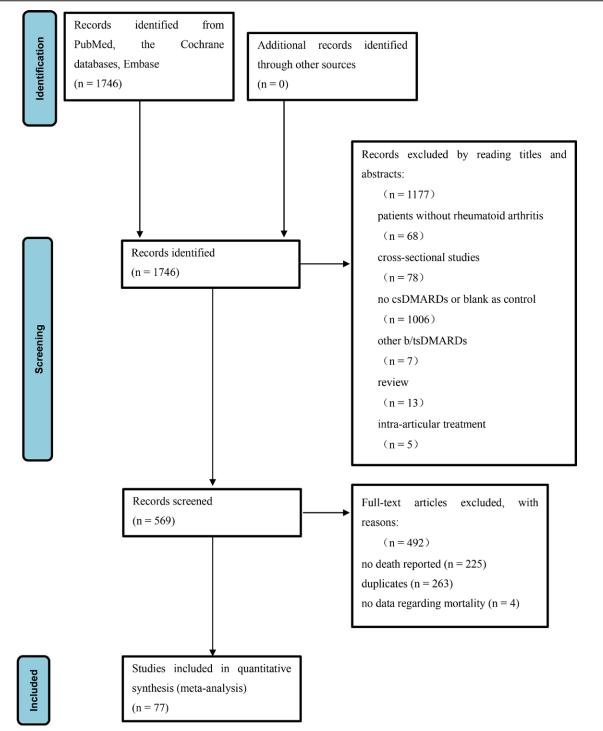
2. Methods

2.1. Literature search

According to the recommendations from the Cochrane Handbook for Systematic Reviews for meta-analysis, we conducted systematic searches in PubMed, the Cochrane databases, Embase, and manual searches of reference lists from systematic reviews and original publications. Studies published in English from January 1, 2000, to August 20, 2021, were selected. The search terms included the following keywords: adalimumab, etanercept, certolizumab pegol, infliximab, golimumab, tofacitinib, baricitinib, upadacitinib, rituximab, tocilizumab, sarilumab, abatacept, rheumatoid arthritis, randomized controlled trial, observational study, cohort study, mortality, and all adults. We limited our search to articles published in the English language and human clinical trials. As the basis of the strategies applied for other electronic databases, we used the PubMed search strategy.

2.2. Inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were as follows: the target population was adults with RA diagnosed according to the 1987 American College of Rheumatology criteria or the 2010 American College of Rheumatology/





EULAR criteria; randomized controlled trial (RCT, observational study and cohort study; interventions that included the bDMARDs or tsDMARDs listed above according to the 2019 EULAR recommendations.^[5] The exclusion criteria

were as follows: studies in which no death reported, studies in which no csDMARDs or blank as control group, and studies in which interventions were delivered through intra-articular treatment.

tudy or Subgroup	b/tsDM/ Events	ARDS Total	non-b/tsDM Events		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
patacept Genovese MC 2005 6m	1	258	<u>events</u>	133	0.1%	1.55 [0.06, 37.84]	
batacept Genovese MC 2005 011 batacept Kremer JM 2005 1y	1	230	0	119	0.1%	1.63 [0.07, 39.68]	
batacept Kremer JM 2006 1y	1	433	1	219	0.2%	0.51 [0.03, 8.05]	
abatacept Weinblatt M 2006 1y	5	856	4	418	0.8%	0.61 [0.16, 2.26]	
abatacept Westhovens R 2009 1y	2	256	4	253	0.6%	0.49 [0.09, 2.67]	
adalimumab Breedveld FC 2006 2y	5	542	1	257	0.2%	2.37 [0.28, 20.19]	
adalimumab Combe B 2021 24w	0	325	2	475	0.3%	0.29 [0.01, 6.06]	
adalimumab Fleischmann R 2019 26w	2	327	2	651	0.2%	1.99 [0.28, 14.07]	
adalimumab Furst DE 2003 24w	1	318	0	318	0.1%	3.00 [0.12, 73.37]	
adalimumab Hørslev-Petersen K 2016 96w	1	89	1	91	0.1%	1.02 [0.06, 16.10]	
adalimumab Kavanaugh A 2013 26w	6	515	1	517	0.1%	6.02 [0.73, 49.86]	
adalimumab Keystone EC 2004 52w	3	419	0	200	0.1%	3.35 [0.17, 64.55]	
adalimumab Miyasaka N 2008 24w	2	265	0	87	0.1%	1.65 [0.08, 34.13]	
adalimumab Smolen JS 2014 78w	3	814	0	112	0.1%	0.97 [0.05, 18.67]	
adalimumab Takeuchi T 2014 26w	0	171	1	163	0.2%	0.32 [0.01, 7.75]	
adalimumab van de Putte 2003 12w	1	214	0	70	0.1%	0.99 [0.04, 24.05]	
adalimumab van de Putte 2004 26w	3	434	1	110	0.2%	0.76 [0.08, 7.24]	
adalimumab van Vollenhoven 2012 6m	1	204	0	108	0.1%	1.60 [0.07, 38.83]	
anti-TNF Lan JL 2017 2y Cohort study	77	1017	72	1017	10.8%	1.07 [0.78, 1.46]	+
anti-TNF Lunt M 2010 cohort study	856	12672	204	3522	47.9%	1.17 [1.01, 1.35]	•
anti-TNF Raaschou P 2011 cohort study	113	302	256	586	26.1%	0.86 [0.72, 1.02]	-
paricitinib Dougados M 2017 24w	0	456	2	228	0.5%	0.10 [0.00, 2.08]	·
oaricitinib Fleischmann R 2017 52w	0	374	3	210	0.7%	0.08 [0.00, 1.55]	•
oaricitinib Genovese MC 2016 24w	1	351	0	176	0.1%	1.51 [0.06, 36.84]	
aricitinib/adalimumab Taylor PC 2017 52w	4	817	1	488	0.2%	2.39 [0.27, 21.31]	— <u> </u>
Certolizumab pegol Emery P 2017 52w	2	655	1	213	0.2%	0.65 [0.06, 7.14]	
Certolizumab pegol Hetland ML 2020 24w	1	203	0	200	0.1%	2.96 [0.12, 72.13]	
Certolizumab pegol Keystone E 2008 52w	6	783	1	199	0.2%	1.52 [0.18, 12.59]	
Certolizumab pegol Kivitz AJ 2014 6w	1	110	0	114	0.1%	3.11 [0.13, 75.49]	
Certolizumab pegol Smolen J 2009 24w	2	492	0	127	0.1%	1.30 [0.06, 26.87]	
Certolizumab pegol Weinblatt ME 2012 12w	2	851	0	212	0.1%	1.25 [0.06, 25.94]	
Certolizumab pegol Yamamoto K 2014 24w	1	116	0	114	0.1%	2.95 [0.12, 71.64]	
etanercept Combe B 2006 24w	1	204	0	50	0.1%	0.75 [0.03, 18.05]	
etanercept Emery P 2010 2y	1	265	1	263	0.2%	0.99 [0.06, 15.78]	
etanercept Genovese MC 2002 24m	2	415	0	217	0.1%	2.62 [0.13, 54.34]	
etanercept Kim HY 2012 16w	1	197	0	103	0.1%	1.58 [0.06, 38.34]	
etanercept Listing J 2005 12m Cohort study	3	858	1	601	0.2%	2.10 [0.22, 20.15]	
etanercept Moreland LW 2012 2y	3	499	1	256	0.2%	1.54 [0.16, 14.72]	
etanercept O'Dell JR 2013 48w	1	175	0	178	0.1%	3.05 [0.13, 74.39]	
etanercept van der Heijde D 2007 3y	4	454	1	228	0.2%	2.01 [0.23, 17.87]	
etanercept Weisman MH 2007 16w	5	266	1	269	0.1%	5.06 [0.59, 42.99]	
jolimumab Keystone EC 2009 24w	1	311	0	133	0.1%	1.29 [0.05, 31.43]	
jolimumab Emery P 2013 52w	3	477	0	160	0.1%	2.36 [0.12, 45.40]	
jolimumab Kay J 2008 52w	1	137	0	35	0.1%	0.78 [0.03, 18.81]	
jolimumab Kremer J 2010 48w	5	514	0	129	0.1%	2.78 [0.15, 49.90]	
jolimumab Smolen JS 2009 24w	0	306	1	155	0.3%	0.17 [0.01, 4.13]	•
olimumab Weinblatt ME 2014 24w	1	395	1	197	0.2%	0.50 [0.03, 7.93]	
nfliximab Abe T 2006 20w	2	100	0	47	0.1%	2.38 [0.12, 48.54]	
nfliximab Leirisalo-Repo M 2013 2y	1	50	0	49	0.1%	2.94 [0.12, 70.50]	
nfliximab Maini RN 2004 102w	8	340	4	88	1.0%	0.52 [0.16, 1.68]	
nfliximab Nam JL 2014 78w	1	55	0	57	0.1%	3.11 [0.13, 74.68]	
nfliximab St Clair EW 2004 54w	2	722	2	282	0.4%	0.39 [0.06, 2.76]	
nfliximab van Vollenhoven 2012 2y	1	128	0	130	0.1%	3.05 [0.13, 74.10]	
nfliximab Westhovens R 2006 22w	4	721	1	363	0.2%	2.01 [0.23, 17.95]	
nfliximab/abatacept Schiff M 2008 28w	2	321	0	110	0.1%	1.72 [0.08, 35.63]	
ituximab Emery P 2010 24w	2	337	1	172	0.2%	1.02 [0.09, 11.18]	
ituximab Emery P 2006 24w	1	316	0	149	0.1%	1.42 [0.06, 34.64]	
ituximab Strand V 2006 2y	1	121	0	40	0.1%	1.01 [0.04, 24.27]	
ituximab Tak PP 2012 104w	3	499	3	249	0.6%	0.50 [0.10, 2.45]	
ituximab Wijesinghe H 2017 24w	0	20	1	20	0.2%	0.33 [0.01, 7.72]	
sarilumab Fleischmann R 2017 24w	0	365	1	181	0.3%	0.17 [0.01, 4.05]	
sarilumab Huizinga TW 2014 12w	1	254	0	52	0.1%	0.62 [0.03, 15.10]	
sarilumab Tanaka Y 2019 52w	4	799	3	398	0.6%	0.66 [0.15, 2.95]	
ocilizumab Burmester GR 2016 52w	7	870	2	287	0.5%	1.15 [0.24, 5.53]	
ocilizumab Genovese MC 2008 24w	2	803	2	413	0.4%	0.51 [0.07, 3.64]	
ocilizumab Jones G 2010 24w	3	286	1	284	0.2%	2.98 [0.31, 28.47]	
ocilizumab Kivitz A 2014 24w	3	437	0	219	0.1%	3.52 [0.18, 67.77]	
ocilizumab Kremer JM 2011 52w	5	797	1	393	0.2%	2.47 [0.29, 21.03]	
ocilizumab Yazici Y 2012 24w	3	409	0	205	0.1%	3.52 [0.18, 67.77]	
ofacitinib Fleischmann R 2012 24w	1	272	0	59	0.1%	0.66 [0.03, 15.99]	
ofacitinib Kremer J 2013 6m	4	633	0	159	0.1%	2.27 [0.12, 41.97]	
ofacitinib Kremer JM 2012 24w	1	440	0	69	0.1%	0.48 [0.02, 11.57]	
ofacitinib Lee EB 2014 24m	4	770	0	186	0.1%	2.18 [0.12, 40.37]	
ofacitinib van der Heijde D 2019 6m	3	637	0	160	0.1%	1.77 [0.09, 34.03]	
Ipadacitinib Genovese MC 2018 12w	1	330	0	169	0.1%	1.54 [0.06, 37.62]	
ıpadacitinib Smolen JS 2019 14w	1	432	0	216	0.1%	1.50 [0.06, 36.75]	
Ipadacitinib van Vollenhoven R 2020 24w	5	631	1	314	0.2%	2.49 [0.29, 21.21]	
Fotal (95% CI)		44227		20201	100.0%	1.08 [0.98, 1.19]	1
Catal avanta	1212		588				
Fotal events							

Figure 2. Forest plot of trials comparing b/tsDMARDs with non-b/tsDMARDs for the risk of all-cause mortality in patients with rheumatoid arthritis. b/tsDMARD = biological/ targeted synthetic disease-modifying antirheumatic drug, CI = confidence interval.

Two investigators (M.D.P. and Z.S.) independently extracted data from articles using a customized form available upon request from the authors. Disagreements were resolved by consensus. This is a systematic review, and ethical approval was not required.

2.3. Data analysis

The Review Manager statistical software package (version 5.3, The Cochrane Collaboration, London, United Kingdom) was used to perform statistical analyses. We conducted this meta-analysis according to the Preferred Reporting Items for

study or Subgroup	iTNF Events	Total	non-b/tsDM Events		Woight	Risk Ratio M-H, Fixed, 95% CI			Risk Ratio -H. Fixed, 95% CI	
dalimumab Breedveld FC 2006 2v	Events 5	542	1	257	2.8%	2.37 [0.28, 20.19]		m	-n, rixeu, 95% Ci	
dalimumab Breedveld FC 2006 Zy dalimumab Combe B 2021 24w	0	325	2	475	4.2%	0.29 [0.01, 6.06]				
dalimumab Combe B 2021 24w dalimumab Fleischmann R 2019 26w	2	325	2	475	4.2%					
	2	327	2	318		1.99 [0.28, 14.07]		_		
Idalimumab Furst DE 2003 24w	1	318	U 1	318	1.0%	3.00 [0.12, 73.37]				
idalimumab Hørslev-Petersen K 2016 96w					2.1%	1.02 [0.06, 16.10]				
Idalimumab Kavanaugh A 2013 26w	6	515	1	517	2.1%	6.02 [0.73, 49.86]		_		
dalimumab Keystone EC 2004 52w	3	419	0	200	1.4%	3.35 [0.17, 64.55]				
idalimumab Miyasaka N 2008 24w	2	265	•	87	1.6%	1.65 [0.08, 34.13]				
dalimumab Smolen JS 2014 78w	3	814	0	112	1.8%	0.97 [0.05, 18.67]				
dalimumab Takeuchi T 2014 26w		171	1	163	3.2%	0.32 [0.01, 7.75]			·	
idalimumab Taylor PC 2017 52w*	1	330	1	488	1.7%	1.48 [0.09, 23.56]	_		-	
dalimumab van de Putte 2003 12w		214	0	70	1.6%	0.99 [0.04, 24.05]				_
idalimumab van de Putte 2004 26w	3	434	1	110	3.3%	0.76 [0.08, 7.24]				
idalimumab van Vollenhoven 2012 6m	1	204	0	108	1.4%	1.60 [0.07, 38.83]				-
ertolizumab pegol Emery P 2017 52w	2	655	1	213	3.1%	0.65 [0.06, 7.14]				_
ertolizumab pegol Hetland ML 2020 24w	1	203	0	200	1.0%	2.96 [0.12, 72.13]				
ertolizumab pegol Keystone E 2008 52w	6	783	1	199	3.3%	1.52 [0.18, 12.59]		_		
ertolizumab pegol Kivitz AJ 2014 6w	1	110	0	114	1.0%	3.11 [0.13, 75.49]				
certolizumab pegol Smolen J 2009 24w	2	492	0	127	1.7%	1.30 [0.06, 26.87]				
ertolizumab pegol Weinblatt ME 2012 12w	2	851	0	212	1.7%	1.25 [0.06, 25.94]			-	
certolizumab pegol Yamamoto K 2014 24w	1	116	0	114	1.1%	2.95 [0.12, 71.64]				
tanercept Combe B 2006 24w	1	204	0	50	1.7%	0.75 [0.03, 18.05]	_			
tanercept Emery P 2010 2y	1	265	1	263	2.1%	0.99 [0.06, 15.78]				
tanercept Genovese MC 2002 24m	2	415	0	217	1.4%	2.62 [0.13, 54.34]				
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tanercept Moreland LW 2012 2y	3	499	1	256	2.8%	1.54 [0.16, 14.72]		_		
tanercept O'Dell JR 2013 48w	1	175	0	178	1.0%	3.05 [0.13, 74.39]				
tanercept van der Heijde D 2007 3y	4	454	1	228	2.8%	2.01 [0.23, 17.87]		-		
tanercept Weisman MH 2007 16w	5	266	1	269	2.1%	5.06 [0.59, 42.99]				
olimumab Keystone EC 2009 24w	1	311	0	133	1.5%	1.29 [0.05, 31.43]				
olimumab Emery P 2013 52w	3	477	0	160	1.6%	2.36 [0.12, 45.40]				
olimumab Kay J 2008 52w	1	137	0	35	1.7%	0.78 [0.03, 18.81]	_			
olimumab Kremer J 2010 48w	5	514	0	129	1.7%	2.78 [0.15, 49.90]		_		
olimumab Smolen JS 2009 24w	0	306	1	155	4.1%	0.17 [0.01, 4.13]	·			
olimumab Weinblatt ME 2014 24w	1	395	1	197	2.8%	0.50 [0.03, 7.93]	_		-	_
nfliximab Abe T 2006 20w	2	100	0	47	1.4%	2.38 [0.12, 48.54]				
nfliximab Leirisalo-Repo M 2013 2y	1	50	0	49	1.1%	2.94 [0.12, 70.50]				
nfliximab Maini RN 2004 102w	8	340	4	88	13.2%	0.52 [0.16, 1.68]		_	-	
nfliximab Nam JL 2014 78w	1	55	0	57	1.0%	3.11 [0.13, 74.68]				
nfliximab Schiff M 2008 28w*	1	165	0	110	1.2%	2.01 [0.08, 48.80]				
nfliximab St Clair EW 2004 54w	2	722	2	282	6.0%	0.39 [0.06, 2.76]			-	
nfliximab van Vollenhoven 2012 2y	1	128	0	130	1.0%	3.05 [0.13, 74.10]				
nfliximab Westhovens R 2006 22w	4	721	1	363	2.8%	2.01 [0.23, 17.95]		-		
otal (95% CI)		15073		8325	100.0%	1.47 [1.02, 2.12]			•	
otal events	93		25							
leterogeneity: Chi ² = 16.37, df = 42 (P = 1.00)	; I* = 0%						0.01	0.1		10
est for overall effect: Z = 2.05 (P = 0.04)							0.01	0.1	iTNF non-b/tsl	

i-TNF

	ilL-6	6	non-b/tsDN	IARDs		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl		
sarilumab Fleischmann R 2017 24w	0	365	1	181	12.4%	0.17 [0.01, 4.05]	•			
sarilumab Huizinga TW 2014 12w	1	254	0	52	5.1%	0.62 [0.03, 15.10]				
sarilumab Tanaka Y 2019 52w	4	799	3	398	24.8%	0.66 [0.15, 2.95]				
tocilizumab Burmester GR 2016 52w	7	870	2	287	18.6%	1.15 [0.24, 5.53]		-		
tocilizumab Genovese MC 2008 24w	2	803	2	413	16.3%	0.51 [0.07, 3.64]				
tocilizumab Jones G 2010 24w	3	286	1	284	6.2%	2.98 [0.31, 28.47]				
tocilizumab Kivitz A 2014 24w	3	437	0	219	4.1%	3.52 [0.18, 67.77]				
tocilizumab Kremer JM 2011 52w	5	797	1	393	8.3%	2.47 [0.29, 21.03]				
tocilizumab Yazici Y 2012 24w	3	409	0	205	4.1%	3.52 [0.18, 67.77]				
Total (95% CI)		5020		2432	100.0%	1.20 [0.62, 2.32]		+		
Total events	28		10							
Heterogeneity: Chi ² = 5.03, df = 8 (P = 0	.75); I ² = (0%					0.01 0.1	1 10 10		
Test for overall effect: Z = 0.53 (P = 0.60	0						0.01 0.1	1 10 10 ilL-6 non-b/tsDMARDs		



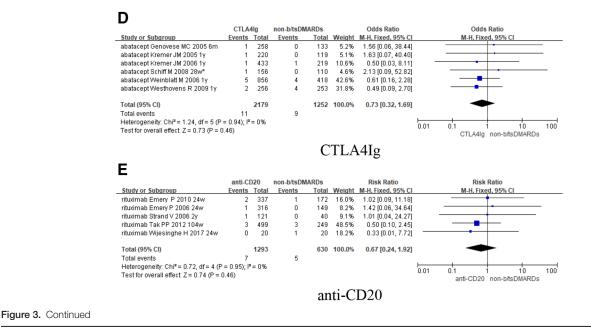
С

В

iJAK		non-b/tsDM	ARDs		Risk Ratio	Risk Ratio		
Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl		
0	456	2	228	20.5%	0.10 [0.00, 2.08]	· · · · · · · · · · · · · · · · · · ·		
0	374	3	210	27.6%	0.08 [0.00, 1.55]	· · · · · · · · · · · · · · · · · · ·		
1	351	0	176	4.1%	1.51 [0.06, 36.84]			
3	487	1	488	6.2%	3.01 [0.31, 28.80]			
1	272	0	59	5.1%	0.66 [0.03, 15.99]			
4	633	0	159	4.9%	2.27 [0.12, 41.97]			
1	440	0	69	5.3%	0.48 [0.02, 11.57]			
4	770	0	186	5.0%	2.18 [0.12, 40.37]			
3	637	0	160	4.9%	1.77 [0.09, 34.03]			
1	330	0	169	4.1%	1.54 [0.06, 37.62]			
1	432	0	216	4.1%	1.50 [0.06, 36.75]			
5	631	1	314	8.2%	2.49 [0.29, 21.21]			
	5813		2434	100.0%	0.98 [0.49, 1.96]	+		
24		7						
² = 0%								
						0.01 0.1 1 10 10 iJAK non-b/tsDMARDs		
	Events 0 0 1 3 1 4 4 1 4 3 1 1 5 24	Events Total 0 456 0 374 1 351 3 487 1 272 4 633 1 440 4 700 3 637 1 330 1 432 5 631 5813 24	Events Total Events 0 456 2 0 374 3 1 351 0 3 487 1 1 272 0 4 633 0 1 440 00 4 770 0 3 637 0 1 330 0 1 432 0 5 631 1 5813 24 7	Events Total Events Total 0 456 2 228 0 374 3 210 1 351 0 176 3 487 1 488 1 272 0 59 4 633 0 159 4 633 0 169 4 770 0 186 3 637 0 169 1 432 0 216 5 631 1 314 5813 2434 7	Events Total Events Total Weight 0 456 2 228 20.5% 0 374 3 210 27.6% 1 351 0 176 4.1% 3 407 1 498 6.2% 1 272 0 59 5.1% 4 633 0 159 4.9% 1 440 0 69 5.3% 4 770 0 186 5.0% 3 637 0 160 4.9% 1 330 0 160 4.1% 5 631 1 314 8.2% 5813 2434 10.0% 2434 10.0%	Events Total Events Total Weight M-H, Fixed, 95% CI 0 456 2 228 20.5% 0.10 (0.00, 2.08) 0 374 3 210 27.6% 0.09 [0.00, 1.65] 1 351 0 176 4.1% 1.51 [0.06, 36.84] 3 407 1 488 6.2% 3.01 [0.31, 28.90] 1 272 0 55 5.1% 0.66 [0.03, 15.99] 4 633 0 159 4.9% 2.27 [0.12, 41.97] 1 440 0 69 5.3% 0.48 [0.02, 11.57] 4 770 0 186 6.0% 2.18 [0.03, 36.62] 1 330 0 160 4.9% 1.77 [0.09, 34.03] 1 330 0 160 4.1% 1.56 [0.06, 37.62] 1 432 0 216 4.1% 1.50 [0.06, 37.62] 5 6.31 1 314 8.2% 2.49 [0.29, 21.21]		

iJAK

Figure 3. The associations between the use of different b/tsDMARDs molecules involved and mortality endpoint. anti-CD20 = anti-cluster of differentiation 20, b/tsDMARD = biological/ targeted synthetic disease-modifying antirheumatic drug, CI = confidence interval, CTLA4Ig = cytotoxic T lymphocyte antigen-4 lg, ilL-6 = interleukin-6 inhibitor, iJAK = janus kinase inhibitor, iTNF = tumor necrosis factor inhibitor.



Systematic Reviews and Meta-Analyses guidelines for conducting and reporting meta-analyses.^[18]

Statistical heterogeneity was tested with an I² statistic calculation.^[19] In the statistical analysis, a high level of heterogeneity was defined as an I² > 50%, whereas a low level of heterogeneity was defined as an I² \leq 50%. For analysis, we used a fixed-effects model. Qualities of the observational studies were evaluated using the Newcastle-Ottawa Scale, and qualities of RCTs were evaluated using the Cochrane risk of bias tool. A third investigator (H.F.Z.) confirmed the accuracy of the abstractions and study quality evaluation.

We performed additional subgroup analyses to determine whether the findings would change substantially. For the subgroup analyses, we divided the studies according to the following: different types of studies (RCTs or cohort studies), rate of clinical application of different molecules (TNF inhibitors, Janus kinase [JAK] inhibitors, interleukin [IL]-6 inhibitors, cytotoxic T lymphocyte antigen-4 [CTLA4] Ig, and anti-CD20 monoclonal antibodies), and study duration (excluding studies <6 months, 1 year, or 2 years). Specific causes of mortality such as infections, malignancy, heart disease, respiratory disease, digestive system disease, cerebral disease, suicide, unknown, and others were analyzed in subgroups.

3. Results

3.1. Summaries of included studies

The flowchart for the study selection process is summarized in Figure 1. Among the initially analyzed 1746 studies, 77 studies fulfilled our inclusion criteria with 73 RCTs and 4 cohort studies, respectively. The RCTs consisted of 4 baricitinib studies^[20-23] (one of which included adalimumab^[22]), 5 tofacitinib studies,^[24-28] 3 upadacitinib studies,^[29-31] 13 adalimumab studies,^[32-44] 7 certolizumab pegol studies,^[45-51] 8 etanercept studies,^[52-59] 6 golimumab studies,^[60-65] 8 infliximab studies^[66-73] (one of which included abatacept^[69]), 3 sarilumab studies,^[74-76] 6 tocilizumab studies,^[77-82] 5 abatacept studies,^[83-87] and 5 rituximab studies.^[88-92] The cohort studies consisted of 4 anti-TNF studies^[93-96] (see Table S1A, B, Supplemental Digital Content, http://links.lww.com/MD/G845, which illustrates baseline characteristics of included studies).

The risk of bias for RCT was systematically evaluated by the Cochrane tool. Most of our comparison analyses indicated the RCTs had a high quality of evidence, and only 5 studies were assessed as high or unclear risk (see Fig. S1A, B, Supplemental Digital Content, http://links.lww.com/MD/G845, which illustrates evaluation for risk of bias in included RCTs). Funnel plots indicated an even distribution for the mean values of the parameters evaluated (see Fig. S2, Supplemental Digital Content, http://links.lww.com/MD/G845, which illustrates the funnel plot of included RCTs). The included cohort studies were of relatively high quality as Newcastle-Ottawa Scale suggested (see Table S2, Supplemental Digital Content, http://links.lww.com/MD/G845, which illustrates evaluation for risk of bias in included cohort studies).

The range of study duration was from 6 weeks to 3 years, and 64,428 patients were included in the analysis. Among these patients, 44,227 were treated with b/tsDMARDs, and 20,201 were treated with non-b/tsDMARDs.

3.2. Primary outcome

3.2.1. Mortality of any cause upon b/tsDMARD compared with non-b/tsDMARDs. During the study duration, 1212 (2.74%) deaths were observed in patients treated with b/tsDMARDs compared to 588 (2.91%) deaths in those treated with non-b/tsDMARDs. Compared with non-b/tsDMARDs users, the risks of mortality were not significantly increased in b/tsDMARDs users (relative risk [RR] = 1.08; 95% confidence interval [CI] = 0.98–1.19; Fig. 2).

3.3. Secondary analyses

3.3.1. Subgroup analyses with respect to molecules involved (TNF inhibitors, JAK inhibitors, IL-6 inhibitors, CTLA4lg and anti-CD20 Ag) in RCTs. When stratified by the molecules involved, subgroup analyses showed significant increase in risks of mortality in anti-TNFs users with RA compared with non-b/tsDMARDs (RR = 1.47,95% CI = 1.02-2.12). But no significant difference was found between other molecules subgroups. We observed the following: in the iIL-6 subgroup: RR = 1.20,95% CI = 0.62-2.32; in the JAK inhibitor subgroup: RR = 0.73,95% CI = 0.32-1.69; and in the anti-CD20 subgroup: RR = 0.67,95% CI = 0.24-1.92 (Fig. 3).

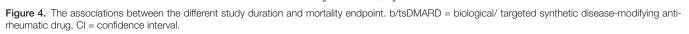
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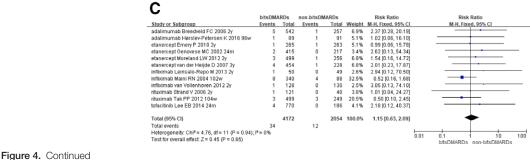
tudy or Subgroup	b/tsDMA Events	Total	non-b/tsDM Events		Weight	Risk Ratio M-H. Fixed, 95% CI	Risk F M-H, Fixe	
batacept Genovese MC 2005 6m	1	258	<u>Events</u>	133	0.7%	1.55 [0.06, 37,84]		
batacept Kremer JM 2005 1v	1	220	ő	119	0.7%	1.63 [0.07, 39.68]		
batacept Kremer JM 2006 1y	1	433	1	219	1.4%	0.51 [0.03, 8.05]		
batacept Weinblatt M 2006 1y	5	856	4	418	5.8%	0.61 [0.16, 2.26]		
batacept Westhovens R 2009 1y	2	256	4	253	4.4%	0.49 [0.09, 2.67]		
dalimumab Breedveld FC 2006 2y	5	542	1	257	1.5%	2.37 [0.28, 20.19]		
dalimumab Combe B 2021 24w	ő	325	2	475	2.2%	0.29 [0.01, 6.06]		
dalimumab Fleischmann R 2019 26w	2	323	2	651	1.4%	1.99 [0.28, 14.07]		
dalimumab Furst DE 2003 24w	1	318	ô	318	0.5%	3.00 [0.12, 73.37]		
dalimumab Hørslev-Petersen K 2016 96w	1	89	1	91	1.1%	1.02 [0.06, 16.10]		
dalimumab Kavanaugh A 2013 26w	6	515	1	517	1.1%	6.02 [0.73, 49.86]	_	
dalimumab Keystone EC 2004 52w	3	419	ó	200	0.7%	3.35 [0.17, 64.55]		
dalimumab Miyasaka N 2008 24w	2	265	ő	87	0.8%	1.65 [0.08, 34.13]		
dalimumab Smolen JS 2014 78w	3	814	ő	112	1.0%	0.97 [0.05, 18.67]		
dalimumab Takeuchi T 2014 26w	0	171	1	163	1.7%	0.32 [0.01, 7.75]		
dalimumab van de Putte 2004 26w	3	434	1	110	1.7%	0.76 [0.08, 7.24]		
dalimumab van Vollenhoven 2012 6m	1	204	ó	108	0.7%	1.60 [0.07, 38.83]		
aricitinib Dougados M 2017 24w	ò	456	2	228	3.6%	0.10 [0.00, 2.08]	·	
aricitinib Fleischmann R 2017 52w	0	374	3	210	4.8%	0.08 [0.00, 1.55]	· · · · · · · · · · · · · · · · · · ·	_
aricitinib Genovese MC 2016 24w	1	351	0	176	4.6%	1.51 [0.06, 36.84]		
aricitinib/adalimumab Taylor PC 2017 52w	4	817	1	488	1.4%	2.39 [0.27, 21.31]		
ertolizumab pegol Emery P 2017 52w	4	655	1	488	1.4%			
	1	203	1	213	0.5%	0.65 [0.06, 7.14]		
ertolizumab pegol Hetland ML 2020 24w	1	203 783	1	200	0.5%	2.96 [0.12, 72.13]		
ertolizumab pegol Keystone E 2008 52w	б 2	783	1	199	1.7%	1.52 [0.18, 12.59]		
ertolizumab pegol Smolen J 2009 24w ertolizumab pegol Yamamoto K 2014 24w	1	492	0	127	0.9%	1.30 [0.06, 26.87] 2.95 [0.12, 71.64]		
								-
anercept Combe B 2006 24w	1	204 265	0	50 263	0.9%	0.75 [0.03, 18.05]		
anercept Emery P 2010 2y	2	415	1	203	0.7%	0.99 [0.06, 15.78]]	
anercept Genovese MC 2002 24m		415				2.62 [0.13, 54.34]		
anercept Moreland LW 2012 2y	3	499	1	256	1.4%	1.54 [0.16, 14.72]		
anercept O'Dell JR 2013 48w	1		0	178	0.5%	3.05 [0.13, 74.39]		
anercept van der Heijde D 2007 3y	4	454	1	228	1.4%	2.01 [0.23, 17.87]		
olimumab Keystone EC 2009 24w	1			133	0.8%	1.29 [0.05, 31.43]		
olimumab Emery P 2013 52w	3	477	0	160	0.8%	2.36 [0.12, 45.40]		
olimumab Kay J 2008 52w	1	137	0	35	0.9%	0.78 [0.03, 18.81]		
olimumab Kremer J 2010 48w	5	514	0	129	0.9%	2.78 [0.15, 49.90]		
olimumab Smolen JS 2009 24w	0	306	1	155	2.2%	0.17 [0.01, 4.13]		
olimumab Weinblatt ME 2014 24w	1	395	1	197	1.4%	0.50 [0.03, 7.93]		
fliximab Leirisalo-Repo M 2013 2y	1	50	0	49	0.5%	2.94 [0.12, 70.50]		
fliximab Maini RN 2004 102w	8	340	4	88	6.9%	0.52 [0.16, 1.68]		_
fliximab Nam JL 2014 78w	1	55	0	57	0.5%	3.11 [0.13, 74.68]		
fliximab St Clair EW 2004 54w	2	722	2	282	3.1%	0.39 [0.06, 2.76]		
fliximab van Vollenhoven 2012 2y	1	128	0	130	0.5%	3.05 [0.13, 74.10]		•
fliximab/abatacept Schiff M 2008 28w	2	321	0	110	0.8%	1.72 [0.08, 35.63]		•
tuximab Emery P 2010 24w	2	337	1	172	1.4%	1.02 [0.09, 11.18]		
tuximab Emery P 2006 24w	1	316	0	149	0.7%	1.42 [0.06, 34.64]		
tuximab Strand V 2006 2y	1	121	0	40	0.8%	1.01 [0.04, 24.27]		
tuximab Tak PP 2012 104w	3	499	3	249	4.3%	0.50 [0.10, 2.45]		
tuximab Wijesinghe H 2017 24w	0	20	1	20	1.6%	0.33 [0.01, 7.72]		
arilumab Fleischmann R 2017 24w	0	365	1	181	2.2%	0.17 [0.01, 4.05]	•	
arilumab Tanaka Y 2019 52w	4	799	3	398	4.3%	0.66 [0.15, 2.95]		
cilizumab Burmester GR 2016 52w	7	870	2	287	3.3%	1.15 [0.24, 5.53]		
cilizumab Genovese MC 2008 24w	2	803	2	413	2.9%	0.51 [0.07, 3.64]		
cilizumab Jones G 2010 24w	3	286	1	284	1.1%	2.98 [0.31, 28.47]		
cilizumab Kivitz A 2014 24w	3	437	0	219	0.7%	3.52 [0.18, 67.77]		
cilizumab Kremer JM 2011 52w	5	797	1	393	1.4%	2.47 [0.29, 21.03]		
cilizumab Yazici Y 2012 24w	3	409	0	205	0.7%	3.52 [0.18, 67.77]		
facitinib Fleischmann R 2012 24w	1	272	0	59	0.9%	0.66 [0.03, 15.99]		
facitinib Kremer J 2013 6m	4	633	0	159	0.9%	2.27 [0.12, 41.97]		· · · · · · · · · · · · · · · · · · ·
facitinib Kremer JM 2012 24w	1	440	0	69	0.9%	0.48 [0.02, 11.57]		
facitinib Lee EB 2014 24m	4	770	0	186	0.9%	2.18 [0.12, 40.37]		
facitinib van der Heijde D 2019 6m	3	637	0	160	0.9%	1.77 [0.09, 34.03]		· · · · · · · · · · · · · · · · · · ·
padacitinib van Vollenhoven R 2020 24w	5	631	ĭ	314	1.4%	2.49 [0.29, 21.21]		
otal (95% CI)		25903		12860	100.0%	1.10 [0.83, 1.46]		•
otal events	144		53				[
eterogeneity: Chi ² = 30.05, df = 62 (P = 1.00)							L	
est for overall effect: $Z = 0.70$ (P = 0.49)							0.01 0.1 1	10 1

study duration $\ge 6m$

В	study duration $\geq 6m$										
Б	b/tsDM/		non-b/tsDN			Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events		Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl			
abatacept Kremer JM 2005 1v	Events	220	Û	119	1.2%	1.63 [0.07, 39.68]		Mi-H, FIXEU, 93% CI	_		
abatacept Kremer JM 2006 Tv	1	433	1	219	2.4%	0.51 [0.03, 8.05]					
abatacept Weinblatt M 2006 1y	5	433	4	418	9.6%	0.61 [0.16, 2.26]					
abatacept Westhovens R 2009 1y	2	256	4	253	9.0% 7.2%	0.49 [0.09, 2.67]	_				
adalimumab Breedveld FC 2006 2v	5	542	1	255	2.4%	2.37 [0.28, 20.19]					
adalimumab Hørslev-Petersen K 2016 96w	1	342	1	257	1.8%	1.02 [0.06, 16.10]					
adalimumab Keystone EC 2004 52w	3	419	0	200	1.2%	3.35 [0.17, 64.55]					
adalimumab Smolen JS 2014 78w	3	814	0	112	1.6%	0.97 [0.05, 18.67]					
baricitinib Fleischmann R 2017 52w	0	374	3	210	8.0%	0.08 [0.00, 1.55]	·				
baricitinib/adalimumab Taylor PC 2017 52w	4	817	1	488	2.2%	2.39 [0.27, 21.31]					
Certolizumab pegol Emery P 2017 52w	2	655	1	213	2.2%	0.65 [0.06, 7.14]					
Certolizumab pegol Keystone E 2008 52w	2	783	1	199	2.7%	1.52 [0.18, 12.59]					
etanercept Emery P 2010 2v	1	265	1	263	1.8%	0.99 [0.06, 15.78]					
etanercept Ernery P 2010 2y etanercept Genovese MC 2002 24m	2	415	Ó	203	1.0%	2.62 [0.13, 54.34]	-				
etanercept Moreland LW 2012 2v	2	415	1	256	2.4%	1.54 [0.16, 14.72]					
etanercept O'Dell JR 2013 48w	3	175	ò	178	0.9%	3.05 [0.13, 74.39]	-				
etanercept van der Heijde D 2007 3v	4	454	1	228	2.4%	2.01 [0.23, 17.87]					
golimumab Emery P 2013 52w	3	477	ò	160	1.3%	2.36 [0.12, 45.40]	-				
golimumab Kay J 2008 52w	3	137	0	35	1.3%	0.78 [0.03, 18.81]					
golimumab Kremer J 2008 52W	5	514	0	129	1.4%	2.78 [0.15, 49.90]					
infliximab Leirisalo-Repo M 2013 2y	5	50	0	49	0.9%	2.94 [0.12, 70.50]	-				
infliximab Maini RN 2004 102w	8	340	4	49	11.4%	0.52 [0.16, 1.68]					
infliximab Nam JL 2014 78w	0	340	0	57	0.9%	3.11 [0.13, 74.68]	-	-			
infliximab St Clair EW 2004 54w	2	722	2	282	5.1%	0.39 [0.06, 2.76]					
infliximab St Clair Eve 2004 54W	2	128	0	130	0.9%	3.05 [0.13, 74.10]	-				
rituximab Strand V 2006 2v	1	120	0	40	1.3%						
rituximab Strand v 2006 2y rituximab Tak PP 2012 104w	3	499	3	249	7.2%	1.01 [0.04, 24.27] 0.50 [0.10, 2.45]	_				
sarilumab Tanaka Y 2019 52w	4	433	3	398	7.2%	0.66 [0.15, 2.95]					
tocilizumab Burmester GR 2016 52w	7	/99 870	2	287	5.4%	1.15 [0.24, 5.53]					
tocilizumab Burmester GR 2016 52W	5	8/0 797	1	287	2.4%	2.47 [0.29, 21.03]					
tofacitinib Lee EB 2014 24m	4	770	0		2.4%		_		_		
totacilinib Lee EB 2014 24m	4	//0	U	186	1.4%	2.18 [0.12, 40.37]					
Total (95% CI)		14345		6404	100.0%	1.03 [0.71, 1.48]		+			
Total events	90		35								
Heterogeneity: Chi ² = 14.26, df = 30 (P = 0.99);	I ² = 0%						0.01 0.1	1 10	100		
Test for overall effect: Z = 0.15 (P = 0.88)								DMARDs non-b/tsDMARD			
							Unto				

study duration $\geq 1y$





3.3.2. Subgroup analyses with respect to the study duration (studies <6 months, 1 year, or 2 years were excluded) in RCTs. For this subgroup analysis, the results suggested no significant difference in the mortality rate between b/tsDMARDs and non-b/tsDMARDs according to different study duration. We observed the following: in the study duration ≥ 6 -month subgroup: RR = 1.10; 95% CI = 0.83–1.46; in the study duration \geq 1-year subgroup: RR = 1.03; 95% CI = 0.71–1.48; in the study duration ≥2-year subgroup: RR = 1.15; 95% CI = 0.63–2.09 (Fig. 4).

3.3.3. Subgroup analyses for mortality of any cause upon b/tsDMARD compared with non-b/tsDMARDs in cohort studies. For this subgroup analysis, the results suggested no significant difference in the mortality rate between b/tsDMARDs and non-b/tsDMARDs in cohort studies. (RR = 1.06; 95% CI = 0.95–1.18; Fig. 5).

3.3.4. Proportion of different causes of death for b/ tsDMARDs and non-b/tsDMARDs in RCTs. In this subgroup analysis, specific causes of mortality (infections, malignancy, heart disease, pulmonary disease, digestive system disease, cerebral disease, suicide, unknown, and others) were evaluated. In both subgroups, the most common cause of mortality was infections and heart disease (Fig. 6).

4. Discussion

In our meta-analysis, we included RCTs and cohort studies covering all the bDMARDs and tsDMARDs recommended by the EULAR.^[5] To our knowledge, this was the largest review of mortality associated with b/tsDMARD therapy in RA. In the meta-analysis, we compared the risk of mortality between b/tsDMARDs and non-b/tsDMARDs. By analyzing the existing data, the use of b/tsDMARDs might not be associated with increased risks of mortality, consistent with previous views.^[16]

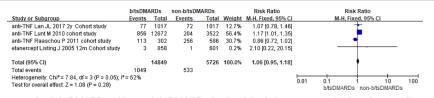
However, the risks of mortality increased in the anti-TNFs treatment group in the subgroup analysis as the data showed. Different from our results, an earlier meta-analysis, including RCTs, found no difference between the 2 therapies.^[17] Another meta-analysis reported that anti-TNFs could even decrease mortality in RA patients.^[14] It is worth noting that the

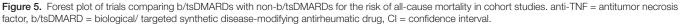
inclusion criteria in these meta-analyses were different from ours. Interventions were limited strictly to anti-TNFs alone and comparators included placebo and csDMARDs in the previous meta-analysis.^[17] While only cohort studies from worldwide biologic registers were included in the another meta-analysis,^[14] patients from the anti-TNFs group and the csDMARD group were not matched mostly. Different from the meta-analysis studies mentioned above, the aim of our study was to compare the risk of all-cause mortality between b/tsDMARDs and non-b/tsDMARDs; all RCTs and cohort studies were included and all the patients involved in b/tsDMARDs treatment were calculated.

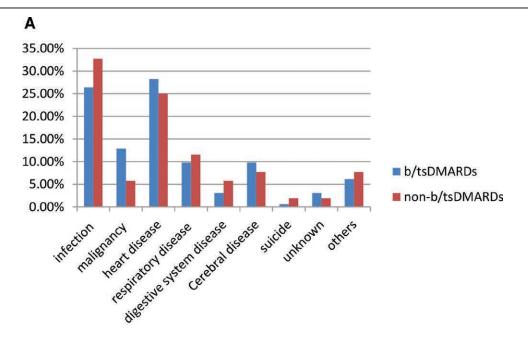
In our study, the leading causes of death in the anti-TNFs or b/tsDMARDs groups were heart disease, followed by infections and malignancy. In terms of the causes of death in RA patients, heart disease seems to be the most important, and the rates in b/tsDMARDs and anti-TNFs were slightly higher than non-b/ tsDMARDs as the histograms showed. Consistent with our findings, possible worsening of cardiovascular function has been reported in anti-TNFs formerly.^[11] However, a meta-analysis published recently indicated that the use of bDMARDs might be associated with the reduced risks of cardiovascular death in RA.^[97] Different retrieval methods and calculation methods may lead to different results. More investigations are needed to validate conclusions.

In both treatment groups, infections was an important causes of death, and the rates in b/tsDMARDs and anti-TNFs were both lower than the control groups to a small degree. As previous data showed, an increase in serious infections might be associated with the anti-TNFs treatment in patients with RA compared to csDMARDs.^[98-100] In terms of mortality, our data indicated that infections were slightly more serious in the non-b/ tsDMARDs treatment.

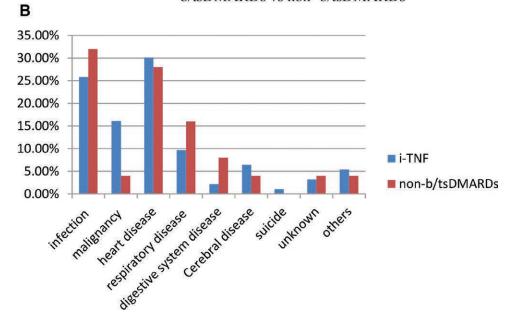
Comparing with the non-b/tsDMARDs, the risk of malignancy in b/tsDMARDs was significantly elevated, especially in anti-TNFs treatment. As reported previously, Published data showed an increase in overall cancer risk in patients on anti-TNFs,^[101] consistent with our results. A 2- to 3-fold increase in risk with a potential dose-dependent relation between treatment and malignancy was observed.[102,103] Due to the short study duration of the RCTs possibly, the proportion of malignancy was <20%. It is worth noting that a recent meta-analysis, in which only a case-control or cohort study was considered,







b/tsDMARDs vs non- b/tsDMARDs



iTNF vs non- b/tsDMARDs

Figure 6. Proportion of different causes of death in b/tsDMARDs and non-b/tsDMARDs in RCTs. b/tsDMARD = biological/targeted synthetic disease-modifying antirheumatic drug, iTNF = tumor necrosis factor inhibitor, RCT = randomized controlled trial.

showed no increased risk of developing cancer overall or some specific subtypes in RA patients with prior cancer receiving biologics.^[104] More investigations are warranted to explore the risk of cancer.

We also performed subgroup analyses based on other molecules (JAK inhibitors, IL-6 inhibitors, CTLA4Ig, and anti-CD20 Ag) and the study duration (>6 months, 1 year, or 2 years). No influence on the risk of mortality in RA patients was found for the 2 treatments in any of these subgroups. Compared with anti-TNFs, studies related to other molecules were lesser relatively. More data regarding these molecules are needed to confirm the influence on mortality. Our study findings should be interpreted with several limitations taken into consideration. First, the studies included in the meta-analysis had a short duration (<3 years) and are therefore not suitable for evaluating delayed-onset events such as long-term mortality. Moreover, results from RCTs may not be transposable to "real life" because patients eligible for RCTs have fewer comorbidities than those encountered in our daily practice. Second, the comparability between the 2 treatment groups decreased in the cohort studies from worldwide biologic registers owing to significant limitations relating to bias and confounding factors. High-quality and long-term controlled clinical trials are needed for further confirmation. Third, the included studies spanned >20 years, and early studies were different from more recent studies in terms of the patients enrolled and the study design, although no effects from publication date bias were found.

5. Conclusion

Our meta-analysis shows that b/tsDMARDs is not associated with a higher risk of mortality due to any cause during RCTs or the cohort studies in patients with RA compared to non-b/ tsDMARDs. While the anti-TNFs treatment increased, the risks of mortality maybe. Further studies are required to assess the long-term effects of b/tsDMARDs on mortality.

Author contributions

HFZ conceptualized this study and designed the systematic review protocol; MDP and ZS performed the study selection and data extraction; ZS performed the statistical analyses; MDP prepared the outlines and wrote the manuscript. All authors contributed to the critical revision of manuscript drafts. Mengduan Pang and Zhe Sun contributed equally to the manuscript.

References

- Nam JL, Takase-Minegishi K, Ramiro S, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2017;76:1113–36.
- [2] Chatzidionysiou K, Emamikia S, Nam J, et al. Efficacy of glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2017;76:1102–7.
- [3] Nishino A, Kawashiri SY, Koga T, et al. Ultrasonographic efficacy of biologic and targeted synthetic disease-modifying antirheumatic drug therapy in rheumatoid arthritis from a multicenter rheumatoid arthritis ultrasound prospective cohort in Japan. Arthritis Care Res (Hoboken). 2018;70:1719–26.
- [4] Choy EH. Effect of biologics and targeted synthetic disease-modifying anti-rheumatic drugs on fatigue in rheumatoid arthritis. Rheumatology (Oxford). 2019;58(Suppl 5):51–v55.
- [5] Smolen JS, LandewéR, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79:685–99.
- [6] Cohen S, Radominski SC, Gomez-Reino JJ, et al. Analysis of infections and all-cause mortality in phase II, phase III, and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014;66:2924–37.
- [7] Michaud TL, Rho YH, Shamliyan T, et al. The comparative safety of tumor necrosis factor inhibitors in rheumatoid arthritis: a meta-analysis update of 44 trials. Am J Med. 2014;127:1208–32.
- [8] Atzeni F, Sarzi-Puttini P, Botsios C, et al. Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: comparison of adalimumab, etanercept and infliximab in the GISEA registry. Autoimmun Rev. 2012;12:225–9.
- [9] Dreyer L, MellemkjærL, Andersen AR, et al. Incidences of overall and site specific cancers in TNFα inhibitor treated patients with rheumatoid arthritis and other arthritides—a follow-up study from the DANBIO Registry. Ann Rheum Dis. 2013;72:79–82.
- [10] Raaschou P, Simard JF, Holmqvist M, et al; ARTIS Study Group. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. BMJ Brit Med J. 2013;346:f1939.
- [11] Generali E, Carrara G, Kallikourdis M, et al. Risk of hospitalization for heart failure in rheumatoid arthritis patients treated with etanercept and abatacept. Rheumatol Int. 2019;39:239–43.
- [12] Dixon WG, Hyrich KL, Watson KD, et al. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2010;69:1086–91.

- [13] Listing J, Kekow J, Manger B, et al. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. Ann Rheum Dis. 2015;74:415–21.
- [14] Forest Divonne M. de La, Gottenberg JE, Salliot C. Safety of biologic DMARDs in RA patients in real life: a systematic literature review and meta-analyses of biologic registers. Joint Bone Spine. 2017;84:133–40.
- [15] Wollenhaupt J, Lee EB, Curtis JR, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. Arthritis Res Ther. 2019;21:89.
- [16] Tarp S, Eric Furst D, Boers M, et al. Risk of serious adverse effects of biological and targeted drugs in patients with rheumatoid arthritis: a systematic review meta-analysis. Rheumatology. 2017;56:417–25.
- [17] Poiroux L, Allanore Y, Kahan A, et al. All-cause mortality associated with TNF-α inhibitors in rheumatoid arthritis: a meta-analysis of randomized controlled trials. Am J Med. 2015;128:1367–1373.e1.
- [18] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
- [19] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
- [20] Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med. 2016;374:1243–52.
- [21] Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis. 2017;76:88–95.
- [22] Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2017;376:652–62.
- [23] Fleischmann R, Schiff M, van der Heijde D, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. Arthritis Rheumatol. 2017;69:506–17.
- [24] Kremer JM, Cohen S, Wilkinson BE, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum. 2012;64:970–81.
- [25] Fleischmann R, Cutolo M, Genovese MC, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum. 2012;64:617–29.
- [26] van der Heijde D, Strand V, Tanaka Y, et al. Tofacitinib in combination with methotrexate in patients with rheumatoid arthritis: clinical efficacy, radiographic, and safety outcomes from a twenty-four-month, phase III study. Arthritis Rheumatol. 2019;71:878–91.
- [27] Kremer J, Li ZG, Hall S, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013;159:253–61.
- [28] Lee EB, Fleischmann R, Hall S, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med. 2014;370:2377–86.
- [29] Vollenhoven R. van, Takeuchi T, Pangan AL, et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naive patients with moderately-to-severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, multi-country, randomized, double-blind, active comparator-controlled trial. Arthritis Rheumatol. 2020;72:1607–20.
- [30] Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet. 2018;391:2513–24.
- [31] Smolen JS, Pangan AL, Emery P, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. Lancet. 2019;393:2303–11.
- [32] Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. 2003;30:2563–71.
- [33] Takeuchi T, Yamanaka H, Ishiguro N, et al. Adalimumab, a human anti-TNF monoclonal antibody, outcome study for the prevention of joint damage in Japanese patients with early rheumatoid arthritis: the HOPEFUL 1 study. Ann Rheum Dis. 2014;73:536–43.

- [34] Smolen JS, Emery P, Fleischmann R, et al. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. Lancet. 2014;383:321–32.
- [35] Hørslev-Petersen K, Hetland ML, ØrnbjergLM, et al. Clinical and radiographic outcome of a treat-to-target strategy using methotrexate and intra-articular glucocorticoids with or without adalimumab induction: a 2-year investigator-initiated, double-blinded, randomised, controlled trial (OPERA). Ann Rheum Dis. 2016;75:1645–53.
- [36] Miyasaka N, CHANGE Study Investigators. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol. 2008;18:252–62.
- [37] Kavanaugh A, Fleischmann RM, Emery P, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. Ann Rheum Dis. 2013;72:64–71.
- [38] van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis. 2004;63:508–16.
- [39] van de Putte LB, Rau R, Breedveld FC, et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis. 2003;62:1168–77.
- [40] Combe B, Kivitz A, Tanaka Y, et al. Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. Ann Rheum Dis. 2021;80:848–58.
- [41] Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50:1400–11.
- [42] Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54:26–37.
- [43] van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367:508–19.
- [44] Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. Arthritis Rheumatol. 2019;71:1788–800.
- [45] Hetland ML, Haavardsholm EA, Rudin A. Active conventional treatment and three different biological treatments in early rheumatoid arthritis: phase IV investigator initiated, randomised, observer blinded clinical trial. BMJ Brit Med J. 2020;371:m4328
- [46] Emery P, Bingham CO 3rd, Burmester GR, et al. Certolizumab pegol in combination with dose-optimised methotrexate in DMARD-naïve patients with early, active rheumatoid arthritis with poor prognostic factors: 1-year results from C-EARLY, a randomised, double-blind, placebo-controlled phase III study. Ann Rheum Dis. 2017;76:96–104.
- [47] Keystone E, Dv H, Mason D Jr, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008;58:3319–29.
- [48] Weinblatt ME, Fleischmann R, Huizinga TW, et al. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. Rheumatology. 2012;51:2204–14.
- [49] Smolen J, LandewéRB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009;68:797–804.
- [50] Yamamoto K, Takeuchi T, Yamanaka H, et al. Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: the HIKARI randomized, placebo-controlled trial. Mod Rheumatol. 2014;24:552–60.
- [51] Kivitz AJ, Schechtman J, Texter M, et al. Vaccine responses in patients with rheumatoid arthritis treated with certolizumab pegol: results from a single-blind randomized phase IV trial. J Rheumatol. 2014;41:648–57.

- [52] Weisman MH, Paulus HE, Burch FX, et al. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. Rheumatology. 2007;46:1122–5.
- [53] Moreland LW, O'Dell JR, Paulus HE, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of early aggressive rheumatoid arthritis trial. Arthritis Rheum. 2012;64:2824–35.
- [54] van der Heijde D, Klareskog L, LandewéR, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum. 2007;56:3928–39.
- [55] Combe B, Codreanu C, Fiocco U, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. 2006;65:1357–62.
- [56] Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002;46:1443–50.
- [57] Kim HY, Hsu PN, Barba M, et al. Randomized comparison of etanercept with usual therapy in an Asian population with active rheumatoid arthritis: the APPEAL trial. Int J Rheum Dis. 2012;15:188–96.
- [58] O'Dell JR, Mikuls TR, Taylor TH, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369:307–18.
- [59] Emery P, Breedveld F, van der Heijde D, et al. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis Rheum. 2010;62:674–82.
- [60] Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009;374:210–21.
- [61] Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum. 2008;58:964–75.
- [62] Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009;68:789–96.
- [63] Emery P, Fleischmann RM, Doyle MK, et al. Golimumab, a human antitumor necrosis factor monoclonal antibody, injected subcutaneously every 4 weeks in patients with active rheumatoid arthritis who had never taken methotrexate: 1-year and 2-year clinical, radiologic, and physical function findings of a phase III, multicenter, randomized, double-blind, placebo-controlled study. Arthritis Care Res. 2013;65:1732–42.
- [64] Kremer J, Ritchlin C, Mendelsohn A, et al. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2010;62:917–28.
- [65] Weinblatt ME, Westhovens R, Mendelsohn AM, et al. Radiographic benefit and maintenance of clinical benefit with intravenous golimumab therapy in patients with active rheumatoid arthritis despite methotrexate therapy: results up to 1 year of the phase 3, randomised, multicentre, double blind, placebo controlled GO-FURTHER trial. Ann Rheum Dis. 2014;73:2152–9.
- [66] Abe T, Takeuchi T, Miyasaka N, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. J Rheumatol. 2006;33:37–44.
- [67] St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004;50:3432–43.
- [68] van Vollenhoven RF, Geborek P, Forslind K, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet. 2012;379:1712–20.
- [69] Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008;67:1096–103.
- [70] Leirisalo-Repo M, Kautiainen H, Laasonen L, et al. Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomised, double-blind, placebo-controlled study (the NEO-RACo Study). Ann Rheum Dis. 2013;72:851–7.

- [71] Nam JL, Villeneuve E, Hensor EM, et al. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treatto-target: a double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the IDEA study). Ann Rheum Dis. 2014;73:75–85.
- [72] Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum. 2004;50:1051–65.
- [73] Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006;54:1075–86.
- [74] Fleischmann R, Adelsberg J. van, Lin Y, et al. Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. Arthritis Rheumatol. 2017;69:277–90.
- [75] Tanaka Y, Wada K, Takahashi Y, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a randomized, placebo-controlled phase III trial in Japan. Arthritis Res Therapy. 2019;21:79.
- [76] Huizinga TW, Fleischmann RM, Jasson M, et al. Sarilumab, a fully human monoclonal antibody against IL-6Rα in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. Ann Rheum Dis. 2014;73:1626–34.
- [77] Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis. 2010;69:88–96.
- [78] Yazici Y, Curtis JR, Ince A, et al. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. Ann Rheum Dis. 2012;71:198–205.
- [79] Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58:2968–80.
- [80] Kivitz A, Olech E, Borofsky M, et al. Subcutaneous tocilizumab versus placebo in combination with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Arthritis Care Res. 2014;66:1653–61.
- [81] Burmester GR, Rigby WF, van Vollenhoven RF, et al. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. Ann Rheum Dis. 2016;75:1081–91.
- [82] Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2011;63:609–21.
- [83] Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005;353:1114–23.
- [84] Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis. 2009;68:1870–7.
- [85] Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006;144:865–76.
- [86] Weinblatt M, Combe B, Covucci A, et al. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. Arthritis Rheum. 2006;54:2807–16.

- [87] Kremer JM, Dougados M, Emery P, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelvemonth results of a phase IIb, double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005;52:2263–71.
- [88] Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis. 2010;69:1629–35.
- [89] Wijesinghe H, Galappatthy P, de Silva R, et al. Leflunomide is equally efficacious and safe compared to low dose rituximab in refractory rheumatoid arthritis given in combination with methotrexate: results from a randomized double blind controlled clinical trial. BMC Musculoskelet Disord. 2017;18:310.
- [90] Strand V, Balbir-Gurman A, Pavelka K, et al. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. Rheumatology. 2006;45:1505–13.
- [91] Tak PP, Rigby W, Rubbert-Roth A, et al. Sustained inhibition of progressive joint damage with rituximab plus methotrexate in early active rheumatoid arthritis: 2-year results from the randomised controlled trial IMAGE. Ann Rheum Dis. 2012;71:351–7.
- [92] Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006;54:1390–400.
- [93] Lan JL, Tseng CH, Chen JH, et al. Reduced risk of all-cancer and solid cancer in Taiwanese patients with rheumatoid arthritis treated with etanercept, a TNF-α inhibitor. Medicine. 2017;96:e6055.
- [94] Listing J, Strangfeld A, Kary S, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum. 2005;52:3403–12.
- [95] Lunt M, Watson KD, Dixon WG, et al. No evidence of association between anti-tumor necrosis factor treatment and mortality in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2010;62:3145–53.
- [96] Raaschou P, Simard JF, Neovius M, Askling J, Anti-Rheumatic Therapy in Sweden Study Group. Does cancer that occurs during or after anti-tumor necrosis factor therapy have a worse prognosis? A national assessment of overall and site-specific cancer survival in rheumatoid arthritis patients treated with biologic agents. Arthritis Rheum. 2011;63:1812–22.
- [97] Hu S, Lin C, Cai X, et al. The biological disease-modifying antirheumatic drugs and the risk of cardiovascular events: a systematic review and meta-analysis. Mediators Inflamm. 2021;2021:7712587.
- [98] Askling J, Fored CM, Brandt L, et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. Ann Rheum Dis. 2007;66:1339–44.
- [99] Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001;345:1098–104.
- [100] Singh JA, Cameron C, Noorbaloochi S, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet. 2015;386:258–65.
- [101] Bongartz T, Warren FC, Mines D, et al. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis. 2009;68:1177–83.
- [102] De Cock D, Hyrich K. Malignancy and rheumatoid arthritis: epidemiology, risk factors and management. Best Pract Res Clin Rheumatol. 2018;32:869–86.
- [103] Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295:2275–85.
- [104] Xie W, Xiao S, Huang Y, et al. A meta-analysis of biologic therapies on risk of new or recurrent cancer in patients with rheumatoid arthritis and a prior malignancy. Rheumatology. 2020;59:930–9.