RESEARCH ARTICLE

Risk of Breast Cancer and Total Malignancies in Rheumatoid Arthritis Patients Undergoing TNF-α Antagonist Therapy: a Meta-analysis of Randomized Control Trials

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Abstract

Context: Interest exits in whether TNF-alpha antagonists increase the risk of breast cancer and total malignancies in patients with rheumatoid arthritis (RA). Objectives: To analyze the risk of malignancies, especially breast cancer, in patients with RA enrolled in randomized control trials (RCTs). Methods: A systematic literature search for RCTs from 1 January 1998 to 1 July 2013 from online databases, such as PubMed, WILEY, EMBASE, ISI web of knowledge and Cochrane Library was conducted. Studies included RCTs that compared the safety of at least one dose of the five TNF-α antagonists with placebo or methotrexate (MTX) (or TNF-α antagonists plus MTX vs placebo plus MTX) in RA patients for more than 24 weeks and imported all the references into document management software EndNote×6. Two independent reviewers selected studies and extracted the data about study design, patients' characteristics and the type, number of all malignancies. Results: 28 RCTs from 34 records with 11,741 patients were analyzed. Of the total, 97 developed at least one malignancy during the double-blind trials, and breast cancer was observed in 17 patients (17.5% of total malignancies). However, there was no statistically significant increased risk observed in either the per protocol (PP) model (OR 0.65, 95%CI [0.22, 1.93]) or the modified intention to treat (mITT) model (OR 0.75, 95%CI [0.25, 2.21]). There were also no significant trend for increased risk of total malignancies on anti-TNF-α therapy administered at approved doses in either model (OR, 1.06, 95%CI [0.64, 1.75], and OR, 1.30, 95%CI [0.80, 2.14], respectively). As to the two models, modified intention to treat model analysis led to higher estimation than per protocol model analysis. Conclusions: This study did not find a significantly increased risk of breast cancer and total malignancies in adults RA patients treated with TNF-α antagonists at approved doses. However, it cannot be ignored that more patients developed malignancies with TNF-α antagonists therapy compared with patients with placebo or MTX, in spite of the lack of statistical significance, so that more strict clinical trials and long-term follow-up are needed, and both mITT and PP analyses should be used in such safety analyses.

Keywords: TNF-α antagonist therapy - rheumatoid arthritis - breast cancer - malignancies - meta analysis

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Introduction

Tumor necrosis factor-α (TNF-α) is a pleiotropic cytokine. Since it reveals both pro- and anti-cancer properties (Balkwill et al., 2009), risk of malignancies in patients undergoing TNF-α antagonists therapy is always controversial. As our previous researches showed, breast cancer over-expressed TNF-α which played a vital role in the cancer's occurrence and development, and we also found transmembrane TNF-α monoclonal antibody (tmTNF-α mAb), as a TNF-α antagonist, effectively suppressed breast cancer growth (Yu et al., 2013). TNF-α antagonists seem offer therapeutic potential in solid tumors. A phase II study had demonstrated the safety and biological activity of Etanercept in metastatic breast cancer (Madhusudan et al., 2004).

However, lots of literatures reported that patients in the duration of TNF-α antagonists therapy developed breast cancer or relapsed (Maini et al., 1999; Bathon et al., 2000; Kremer et al., 2003; Keystone et al., 2004; Maini et al., 2004; Klareskog et al., 2004; Goekoop-Ruiterman et al., 2005; Klareskog et al., 2006; Van der Heijde et al., 2006; Genta et al., 2006; Keystone et al., 2009; Emery et al., 2009; Kremer et al., 2010; Van der Heijde et al., 2010; Keystone et al., 2010; Keystone et al., 2012; Moreland et al., 2012; Weinblatt et al., 2012;

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Emery et al., 2013; Keystone et al., 2013; Takeuchi et al., 2013; Weinblatt et al., 2013). It appears to contradiction about the interrelation between TNF-α antagonists and breast cancer. So we conduct this Meta-analysis of RCTs to define whether the risk of breast cancer is increased statistically in RA patients treated with TNF-α antagonists. And we also assess the total malignancies risk of TNF-α antagonists therapy, as the US Food and Drug Administration (FDA) has warned for thrice.

As the case stands, there has been already several meta-analyses published assessing the therapeutic safety of one or more of the five TNF-α antagonists, but the outcomes of malignancies risk are not always the same (Bongartz et al., 2006; Bongartz et al., 2009; Singh et al., 2009; Wiens et al., 2009; Aaltonen et al., 2012; Lopez-Olivo et al., 2012; Moulis et al., 2012; P et al., 2012; Wong et al., 2012). Most of the metaanalyses were conducted in modified intention to treat model (mITT) (Bongartz et al., 2009; Ni1 et al., 2012; Moulis et al., 2012), which could lead to overestimate compared with per protocol (PP). In addition to lymphoma (Wong et al., 2012) and non-melanoma skin cancers (NMSC) (P et al., 2012), there were no systematic reviews or metaanalyses assessing risk of individual cancer during TNF-α antagonists therapy in patients with RA. We conducted this Meta-analysis for the first time, to our knowledge, assessing the risk of breast cancer in which we are interested, and we used both mITT and PP models.

According to FDA, TNF-α antagonists approved for drugs included, etanercept (1998), infliximab (1998), adalimumab (2002), certolizumab pegol (2008) and golimumab (2009), and their approved doses used in RA therapy were, respectively, etanercept (subcutaneously injection (sc) 25 mg twice a week (biw), or 50 mg weekly), infliximab (adults, intravenously infusion (iv) 3 mg/kg every two months), adalimumab (sc, 40 mg every other week (eow)), certolizumab pegol (sc, 200mg eow, or 400 mg monthly for maintenance), golimumab (sc, 50 mg monthly). One or more of the five drugs were approved to treat the diseases, Rheumatoid arthritis (RA), Inflammatory bowel disease (IBD), Ankylosing spondylitis (AS), Psoriatic arthritis (PsA) and so on. This study we selected RCTs where at least one of the five TNF-α antagonists were used to RA therapy, which could be treated by all the five drugs and also the most wildly used, to assess the breast cancer and total malignancies risk of TNF-α antagonists therapy in patients with RA. The main objection of this study was to assess the breast cancer and total malignancies risk in RA patients treated with TNF-α antagonists at approved doses. And we also conducted analysis to low doses and high doses compared with the approved doses to assess the possible doses-effect relation.

Materials and Methods

Study selection, evaluation of inclusion criteria, data extraction and statistical analysis were conducted based on the Cochrane handbook (Higgins et al., 2008). This article was finished on the basis of QUOROM statement (Moher et al., 1999).

Data sources and search strategy

We searched literatures from online databases including PubMed, WILEY, EMBASE, ISI Web of Knowledge and Cochrane Library, from 1 January 1998 to 1 July 2013 by terms as follow: "etanercept", "infliximab", "certolizumab", "adalimumab", "golimumab", "Rheumatoid arthritis", "randomized controlled trial" OR randomized OR randomly, "clinical trial", "multicenter studies".

To obtain the unpublished trials, we also searched the electronic abstract databases of the annual scientific meetings of both the European League Against Rheumatism and the American College of Rheumatology to date. We referred to the references of those metaanalyses assessing the safety of TNF-α antagonists therapy published in Medline and Cochrane database to supple the possible omission. All the search process was conducted by two independent reviewers (Wei Fan and Hao Chen), and the disagreements were resolved by consensus. In addition, sponsors were contacted for the original detailed protocols.

Study selection

We included randomized, double-blind, placebo/MTX-controlled trials of the five currently licensed TNF-α antagonists. Adults patients enrolled into the trials were diagnosed as active RA according to American College of Rheumatology criteria (Arnett et al., 1989), and had to be randomly allocated to treatment group receiving at least one dose of the five TNF-α antagonists *vs* control group with placebo/MTX (or TNF-α antagonists plus MTX *vs* placebo plus MTX) for more than 24 weeks. We excluded studies as follow: 1) Juvenile idiopathic RA patients received TNF-α antagonists therapy; 2) Open-label studies, or open-label extension periods of RCTs which resulted in a possible diagnosis bias; 3) Studies with no description of adverse events (AEs) or insufficiency; 4) Duration of treatment less than 24 weeks.

Data extraction and quality assessment

Study selection and data extraction were finished by the two independent reviewers mentioned above, and the disagreements were resolved by consensus or the third reviewer, if possible. From each trial included, we extracted information about patients' characteristics, study design, type, and number of all malignancies. We merged the same RCTs or RCTs which actually were different periods of a RCT into one RCT. The quality of studies was assessed with Jadad scale ranging from 0 to 5 points (low quality study: 0-2; high quality: 3-5) (Jadad et al., 1996).

Statistical analyses

Statistical analysis was performed with Review Manager (version 5.0, Cochrane Collaboration, Oxford, UK). Based on the adverse event analysis, the number of patients developing at least one malignancy was what we needed to compared with the total patients receiving at least one dose of the study drugs. We conducted this meta-analysis in both mITT and PP models to analyze. Results were expressed as odds ratios (ORs) and their 95% confidence intervals (CIs), and heterogeneity between

studies was calculated by I^2 and X^2, with the significance level set at 0.05. Then we adopted fixed-effect model and calculated the pooled estimate using Mantel-Haenszel methods (M-H). Since there were null values in some studies without any malignancies developed, continuity correction estimate of the OR was used (J Sweeting et al., 2004), namely, a constant value of 0.5 was added to each number.

Results

Search results

We imported all the records into EndNote×6, and 720 records were left after auto-deduplicated. By reading the titles and abstracts, 559 records were excluded, 161 records left to find the full-text for eligibility. Of the 161 articles, 34 containing 28 trials met our inclusion criterion (Figure 1). Ten trials were excluded because of the duration of treatment less than 24 weeks. In five trials, malignancies were unclear and only one trial that we got the details by sending emails to the authors. Twenty three open-label trials were excluded, and we also excluded the open-label periods following up the double-blind trials in case of diagnosis bias. Eleven trials were excluded, because the control groups were not placebo or MTX. Other exclusion reasons included subanalysis or review (n=20), no adverse event (n=33), unblind or juvenile RA (n=26).

Studies characteristics

Twenty-eight RCTs with 11741 patients were included, and the drugs were etanercept in 6 trials, infliximab in 5 trials, certolizumab pegol in 4 trials, adalimumab in 8 tirals, and golimumab in 5 trials (Table 1).

Dosages for each drug in each trial were multiple. Dosages in etanercept were 10 mg and 25mg biw, or 50mg

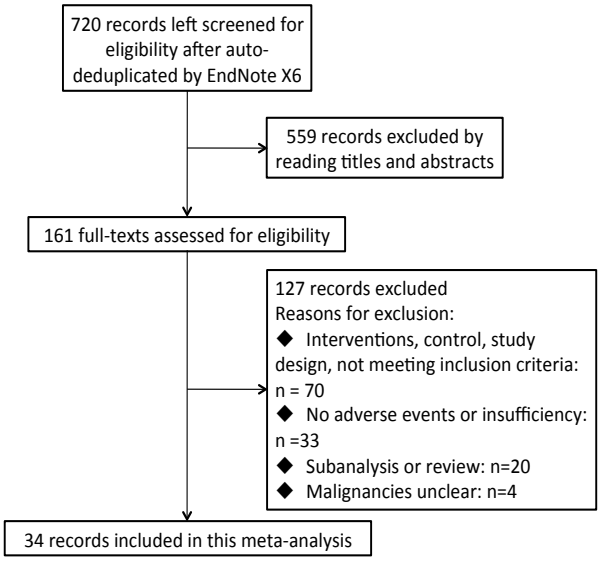

Figure 1. Flow Chart Illustrating the Process of Studies Selection

Table 1. Risk of Total Malignancies in Each Trial Per Protocol Model

First author	Year	Country	Type of TNF-α antagonists	No. of malignancies/ No. of participants randomized		Odds Ratio (95%CI)	Continuity correction* OR (95%CI)
				Treatment	Control		
Moreland	1999	USA	ETA	1/59	0/26	1.36(0.05,34.47)	1.35(0.05,34.19)
Weinblatt	1999	USA	ETA	0/57	0/24	NE	0.43(0.01,21.98)
Bathon	2000	USA	ETA	3/193	2/202	1.58(0.26,9.55)	1.40(0.27,7.18)
Van der Heijde	2007	Netherlands	ETA	9/301	2/119	1.80(0.38,8.47)	1.53(0.37,6.25)
Emery	2008	UK	ETA	4/221	4/189	0.85(0.21,3.46)	0.85(0.35,2.08)
Takeuchi	2013	Japan	ETA	2/151	2/123	0.81(0.11,5.85)	0.81(0.14,4.77)
Maini	1998	UK	INF	0/21	0/6	NE	0.30(0.01,16.78)
Maini	2004	UK	INF	1/47	1/14	0.28(0.02,4.83)	0.29(0.03,3.02)
St Clair	2004	USA	INF	0/323	0/245	NE	0.76(0.01,38.40)
Quinn	2005	UK	INF	0/9	0/10	NE	1.11(0.02,61.37)
Schiff	2008	USA	INF	2/141	1/104	1.48(0.13,16.57)	1.24(0.16,9.52)
Keystone	2008	Canada	CZP	7/255	1/43	1.19(0.14,9.88)	0.86(0.14,5.08)
Fleischmann	2009	USA	CZP	0a/76	0/28	NE	0.37(0.01,19.26)
Smolen	2009	Austria	CZP	1/174	1/17	0.09(0.01,1.55)	0.10(0.01,1.02)
Choy	2012	UK	CZP	0/98	0/65	NE	0.67(0.01,33.92)
Weinblatt	2003	USA	ADA	0/50	0/18	NE	0.37(0.01,16.13)
Furst	2003	USA	ADA	1/290	0/288	2.90(0.12,73.69)	2.99(0.12,73.70)
Breedveld	2006	Netherlands	ADA	6/370	4/169	0.68(0.19,2.44)	0.66(0.19,2.21)
Kim	2007	USA	ADA	0/51	0/40	NE	0.79(0.02,40.49)
Miyasaka	2008	Japan	ADA	0/75	2/80	0.21(0.01,4.40)	0.23(0.01,5.03)
Bejarano	2008	UK	ADA	0/50	0/36	NE	0.72(0.01,37.30)
Detert	2013	Germany	ADA	0/82	3/73	0.12(0.01,2.40)	0.12(0.01,2.36)
Kavanaugh	2013	USA	ADA	2/466	0/460	4.96(0.24,103.53)	4.96(0.24,103.54)
Kay	2008	USA	GLM	1/29	0/21	2.26(0.09,58.32)	2.30(0.10,58.21)
Emery	2009	UK	GLM	1/150	2/150	0.50(0.04,5.54)	0.61(0.04,4.99)
Keystone	2010	Canada	GLM	1/109	1/84	0.77(0.05,12.47)	.80(0.05,12.60)
Tanaka	2012	Japan	GLM	0b/81	0/84	NE	1.04(0.02,52.88)
Hagashi	2013	Japan	GLM	0/8	0/6	NE	0.77(0.01,43.95)

Abbreviations: ETA, etanercept; INF, infliximab; CZP, certolizumab pegol; ADA, adalimumab; GLM, golimumab; NE, negative; CI, confidence interval; OR, Odds Ratio; No., number. *Continuity correction was conducted by adding a constant 0.5 to each cell; a. Two benign neoplasm (1 uterine fibroids and 1 benign parathyroid tumor) were not included; b.One neoplasm(thoracic vertebra tumor) was not included, because it was considered as "borderline" or low malignancy potential

weekly, since 25 mg biw or 50 mg weekly were approved doses, we considered 10 mg biw as low doses, and no high doses were administered; infliximab, dosages were 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, every 4 weeks (q4wk) or every 8 weeks (q8wk), as 3 mg/kg q8wk was approved doses, we considered 1 mg/kg q4wk as low doses and 3 mg/kg q4wk, 6 mg/kg q8wk, 10 mg/kg q4 or q8wks as high doses; certolizumab pegol, dosages were 200 mg, 400 mg, q2wk or q4wk, 400 mg q4wk and 200 mg q2wk were approved, so we considered 400 mg q2wk as high doses, and no low doses were administered; adalimumab, dosages were 20 mg, 40 mg, 80 mg, eow, 40mg eow was approved, so 20 mg eow and 80 mg eow were low and high doses, respectively; golimumab, dosages were 50 mg, 100 mg, q2wk or q4wk, as 50 q4wk was approved, 50 or 100 mg q2wk and 100 mg q4wk were considered as high doses, and no low doses were administered. In one trial (Weinblatt et al., 2013), patients treated with golimumab were administered intravenously 2 mg/kg every 8 weeks, which were excluded from the analysis for irregular route of administration; in this trial, 1 breast cancer was developed in treatment group.

Of the total 11741 patients, treatment groups including different doses were 7780, and 6252 completed the double-blind trials, on the other hands, control groups were 3961, with 2721 completion. No matter of doses, 71 malignancies were developed on TNF-α antagonists and 26 on placebo, and breast cancer was 10 *vs* 7.

Total malignancies and breast cancer

In PP analysis, there were no statistically significant increased risk of breast cancer (OR 0.65, 95%CI [0.22, 1.93]) and total malignancies (1.06[0.64, 1.75]) in RA patients with TNF-α antagonists therapy at approved doses (Table 1 and Table 3), the same as at low doses (OR 0.54, 95%CI [0.09, 3.13] ,OR 0.46, 95%CI [0.13, 1.56], respectively) and high doses (OR 1.61, 95%CI [0.30, 8.78], OR 1.88, 95%CI [0.89, 3.99], respectively) (Table 3). In mITT analysis, the risk of total malignancies at high doses seems to be increased (OR 2.39, 95%CI [1.13, 5.05]) (Table 3), while the breast cancer risk stills no significance (OR 1.74, 95%CI [0.32, 9.44]). Our outcome of total malignancies risk with high doses in mITT analysis was similar with Bongartz et al, (2009) (OR 4.3, 95%CI [1.6, 11.8]), but different with Moulis et al (Moulis et al., 2012)

Table 3. Risk of Breast Cancer and Total Malignancies at Different Doses in Both Models

Doses	Model	Total malignancies	Breast cancer
Low doses	mITT	0.53(0.16,1.80)	0.64(0.11,3.71)
	PP	0.46(0.13,1.56)	0.54(0.09,3.13)
Doses approved	mITT	1.30(0.80,2.14)	0.75(0.25,2.21)
	PP	1.06(0.64,1.75)	0.65(0.22,1.93)
High doses	mITT	2.39(1.13,5.05)	1.74(0.32,9.44)
	PP	1.88(0.89,3.99)	1.61(0.30,8.78)
All doses	mITT	1.37(0.87,2.17)	0,70(0.27,1.82)
	PP	1.12(0.70,1.78)	0.61(0.24,1.59)

Table 2. Risk of Total Malignancies in Each Trial in Modified Intention to Treat Model

First author	Year	Country	Type of TNF-α antagonists	No. of malignancies/ No. of participants randomized		Odds Ratio (95%CI)	Continuity correction* OR (95%CI)
				Treatment	Control		
Moreland	1999	USA	ETA	1/78	0/80	3.12(0.13,77.66)	3.12(0.13,77.71)
Weinblatt	1999	USA	ETA	0/59	0/30	NE	0.51(0.01,26.50)
Bathon	2000	USA	ETA	3/207	2/217	1.58(0.26,9.56)	1.48(0.29,7.54)
Van der Heijde	2007	Netherlands	ETA	9/454	2/228	2.29(0.49,10.67)	1.93(0.48,7.85)
Emery	2008	UK	ETA	4/274	4/268	0.98(0.24,3.95)	0.98(0.26,3.64)
Takeuchi	2013	Japan	ETA	2/182	2/176	0.97(0.13,6.94)	0.97(0.17,5.65)
Maini	1998	UK	INF	0/29	0/14	NE	0.49(0.01,20.08)
Maini	2004	UK	INF	1/86	1/88	1.02(0.06,16.63)	1.02(0.10,10.03)
St Clair	2004	USA	INF	0/373	0/298	NE	0.80(0.02,40.41)
Quinn	2005	UK	INF	0/10	0/10	NE	1(0.02,55.26)
Schiff	2008	USA	INF	2/165	1/110	1.34(0.12,14.93)	1.12(0.15,8.58)
Keystone	2008	Canada	CZP	7/393	1/199	4.17(0.51,34.18)	2.57(0.44,14.94)
Fleischmann	2009	USA	CZP	0/111	0/109	NE	0.98(0.02,49.95)
Smolen	2009	Austria	CZP	1/246	1/127	0.51(0.03,8.29)	0,52(0.05,5.00)
Choy	2012	UK	CZP	0/126	0/121	NE	0.96(0.02,48.76)
Weinblatt	2003	USA	ADA	0/67	0/62	NE	0.93(0.02,47.37)
Furst D E	2003	USA	ADA	1/318	0/318	3.01(0.12,74.15)	3.01(0.12,74.14)
Breedveld	2006	Netherlands	ADA	6/541	4/257	0.71(0.20,2.54)	0.68(0.20,2.30)
Kim H Y	2007	USA	ADA	0/65	0/63	NE	0.97(0.02,49.60)
Miyasaka	2008	Japan	ADA	0/91	2/87	0.19(0.01,3.95)	0.18(0.01,3.95)
Bejarano	2008	UK	ADA	0/75	0/73	NE	0.97(0.02,49.75)
Detert	2013	Germany	ADA	0/87	3/85	0.13(0.01,2.65)	0.14(0.01,2.75)
Kavanaugh	2013	USA	ADA	2/525	0/517	4.94(0.24,103.20)	4.94(0.24,103.23)
Kay	2008	USA	GLM	1/35	0/35	3.09(0.12,78.41)	3.09(0.12,78.41)
Emery	2009	UK	GLM	1/159	2/160	0.50(0.04,5.57)	0.60(0.08,4.60)
Keystone	2010	Canada	GLM	1/89	1/133	1.50(0.09,24.30)	1.50(0.15,14.61)
Tanaka	2012	Japan	GLM	0/86	0/88	NE	1.02(0.02,52.14)
Hagashi	2013	Japan	GLM	0/6	0/8	NE	1.31(0.02,75.11)

Abbreviations: ETA, etanercept; INF, infliximab; CZP, certolizumab pegol; ADA, adalimumab; GLM, golimumab; NE, negative; CI, confidence interval; OR, Odds Ratio; No., number. *Continuity correction was conducted by adding a constant 0.5 to each cell; a. Two benign neoplasm (1 uterine fibroids and 1 benign parathyroid tumor) were not included; b.One neoplasm(thoracic vertebra tumor) was not included, because it was considered as "borderline" or low malignancy potential

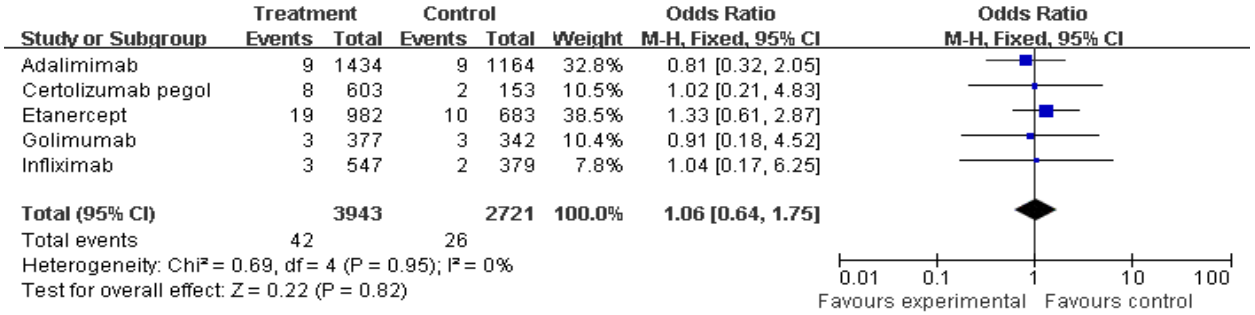

Figure 2. Per Protocol Meta-Analysis of Total Malignancies Risk of TNF-α Antagonists Therapy Used at Doses Approved in RA Patients

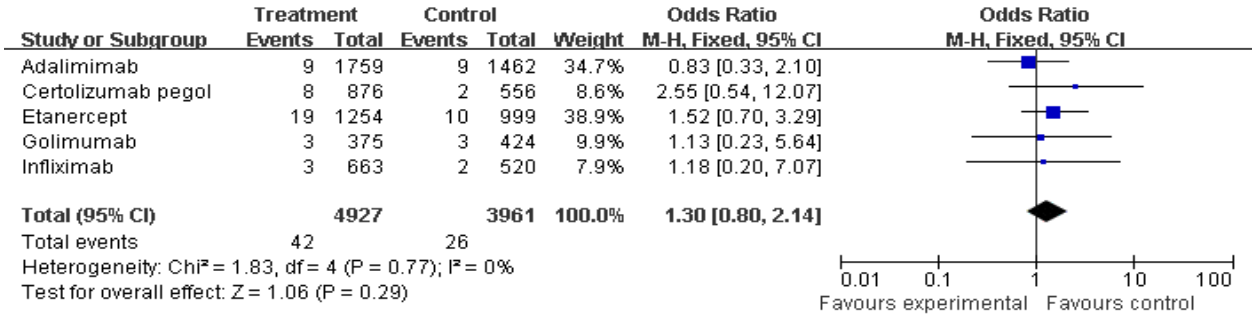

Figure 3. Modified Intention to Treat Meta-Analysis of Total Malignancies Risk of TNF-α Antagonists Therapy Used at Doses Approved in RA Patients

(OR 1.56, 95%CI [0.78, 3.12]). As to the two models, modified intention to treat model analysis led to higher estimation than per protocol model analysis. Egger's test did not show a publication bias, and no heterogeneity was found (I^2= 0) (Figure 2 and Figure 3).

There were no significant differences among the five drugs at approved doses about risk of malignancies (p=0.82 in PP, p=0.29 in mITT) and breast cancer (p=0.30, p=0.60, respectively).

Discussion

A recent study (Tripsianis et al., 2013) demonstrated that patients with primary breast cancer over-expressed TNF-α and anti-TNF-α might be effective. However, the safety of anti-TNF-α therapy was seldom investigated. We conducted this meta-analysis with both mITT and PP models to assess the breast cancer and total malignancies risk of the five TNF-α antagonists therapy in RA patients at different doses. We pooled the results from 28 RCTs with 11741 patients for therapy duration for more than 24 weeks. There was no statistically significant increased risk of breast cancer in both models by means of different doses of TNF-α antagonists *vs* placebo or MTX. In PP analysis, increased risk of total malignancies was not significant, but in mITT analysis, risk of malignancies with high doses TNF-α antagonists therapy notablely increased.

There were several previously published reports reviewing the risk of malignancies, including one for lymphoma and one for non-melanoma skin cancer, in RA patients with TNF-α antagonists therapy. However, there was only one meta-analysis (Moulis et al., 2012), to our knowledge, conducting the per protocol analysis which was considered as more eligible for safety analyses for all the patients included to analysis exposing to the drugs all the study times. In that meta-analysis, they included 33 RCTs to assess the cancer risk of the five TNF-α antagonists therapy with RA patients in PP model comparing with mITT. Of the 33 RCTs, 4 were excluded during our study selection, because 3 RCTs' (Abe et al., 2006; Weisman et al., 2007; Chen et al., 2009) double-blind periods less than 24 weeks, and 1 RCT (Taylor et al., 2004) did not mention adverse events, in which they considered the cancer as 0. Our outcomes of total malignancies risk were similar to their in PP model, but in mITT model, we found a significant increased risk of total malignancies at high drugs doses, while their analysis showed no significance. It may result from the different inclusion criterion and deviation of data extraction. And the malignancies we considered not included the benign neoplasm developed in two RCTs (Fleischmann et al., 2009; Tanaka et al., 2012).

To avoid the diagnosis bias, we excluded open-label trials or periods of open-label extension following up double-blind, in which many patients developed breast cancer after therapy (Kremer et al., 2003; Klareskog et al., 2006; Van der Heijde et al., 2010; Weinblatt et al., 2011; Keystone et al., 2012; Emery et al., 2013; Keystone et al., 2013; Keystone et al., 2013) , and patients in one trial excluded developed breast cancer, of which we could not obtain the details. For those reason, it may result in underestimation of the risk of breast cancer.

Our study has several limitations. Four trials were excluded grudgingly for the publications not providing enough details in their reports. AS the language limited, we included records only in English, which led to underestimation in our results. But no evidence of publications bias was detected in our analysis. Some studies conducted open-label trials immediately after patients completed the double-blind periods, we did not

include the malignancies developed in the follow-up open-label trials. It was annoying that sometimes data from RCTs were not always generalizable, dosages of the drugs administered were always mutative during the studies, which led to the comparison irrigorous and deviation of data extraction.

Overall, we do not find a increased risk of total malignancies and breast cancer in RA patients undergoing TNF-α antagonists at approved doses for at least 24 weeks. It seems safe for RA patients to receive the TNF-α antagonists therapy at doses in line with New Drug Approval. However, it can't be ignored that more patients developed malignancies with TNF-α antagonists therapy compared with patients with placebo or MTX, in spite of no statistical significance. More strait clinical trials and long-term follow-up are needed, and both models should be applied.

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