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ORIGINAL ARTICLE

Adverse drug events associated with 5mg versus 10mg Tofacitinib (Janus kinase inhibitor) twice daily for the treatment of autoimmune diseases: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Several recently published clinical trials have shown tofacitinib to be effective in the treatment of autoimmune diseases. This drug is commonly prescribed either in a 5-mg or in a10-mg dosage twice daily. In this review, we aimed to systematically compare the adverse drug events which were observed with 5 mg versus 10 mg tofacitinib for the treatment of autoimmune diseases. MEDLINE, EMBASE, the Cochrane library, and www.ClinicalTrials.gov were searched (from March to April 2018) for suitable English publications (published before April 2018). The inclusion criteria were as follows: randomized controlled trials, autoimmune disorders (rheumatic arthritis, psoriatic arthritis, moderate to severe psoriasis, and ankylosing spondylitis), and comparison of adverse drug events associated with 5 mg versus 10 mg tofacitinib. This study had follow-up time periods of 3 months and ≥ 6 months. Statistical analysis was carried out by RevMan 5.3 whereby risk ratios (RRs) and 95% confidence intervals (CIs) were generated. A total number of 4287 participants were included (2144 versus 2143 participants who received 5 mg and 10 mg tofacitinib twice daily respectively). The results showed that at 3 months, similar risks of adverse drug events, serious adverse events, and adverse events leading to drug discontinuation were observed with 5 mg versus 10 mg tofacitinib (RR 1.04, 95% CI 0.98–1.10; $P = 0.17$, $I^2 = 0\%$; RR 1.06, 95% CI 0.77–1.48; $P = 0.71$, $I^2 = 0\%$; and RR 1.06, 95% CI 0.78–1.43; $P = 0.73$, $I^2 = 32\%$, respectively). The other outcomes including serious infection events, adjudicated herpes zoster infection, adjudicated opportunistic infection, mild and severe neutropenia, malignancies, and adjudicated major adverse cardiovascular events were also similarly manifested. However, a decreased level of hemoglobin significantly favored 5 mg tofacitinib (RR 1.75, 95% CI 1.19–2.58; $P = 0.005$, $I^2 = 49\%$). Even at a follow-up time period of ≥ 6 months, adverse drug events, serious adverse events, adverse drug events leading to drug discontinuation, and serious infection were still similarly observed. According to this current review, both dosages of tofacitinib were safe to use. Even if similar adverse drug events were observed with 5 mg versus 10 mg tofacitinib twice daily for the treatment of autoimmune disorders, anemia was more prominent with 10 mg tofacitinib at a 3 month follow-up. Nevertheless, future studies based on a larger population size with longer follow-up time periods should further be considered.

Keywords Adverse drug events · Anemia · Autoimmune disorders · Janus kinase inhibitor · Tofacitinib

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Introduction

In this rapidly progressing world, immense development has been made in the medical therapeutic sections. Recently, Janus kinase inhibitors (JAK inhibitors) have shown to be effective in treating autoimmune diseases [1]. One of their mechanisms of action is based on the inhibition of the activity of one or more of the Janus kinase family of enzyme, thus interfering with certain specific pathways, particularly the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway [2].

Tofacitinib, which inhibits the JAK3 enzyme, has been the first JAK inhibitor to reach clinical trials. It is the first JAK inhibitor to have been approved for the treatment of autoimmune disorders such as rheumatic arthritis, psoriatic arthritis, and ankylosing spondylitis followed by baricitinib [3]. While other JAK inhibitors are still being tested for their potential efficacy and safety to treat autoimmune disorders in phase II and III trials, current emphasis should be made on the abovementioned recently approved JAK inhibitors.

Introduction of JAK inhibitors was necessary because even if treatment with biologic agents resulted in suppression of disease for many patients with autoimmune disorders, only approximately 30% achieved complete remission. Another shortcoming of the biologic agents was the fact that majority of the patients experienced disease exacerbation following cessation of treatment [4]. Oral route of administration of drug might also be a preference for patients with rheumatoid arthritis [5].

Several recently published clinical trials have shown tofacitinib to be effective in treating autoimmune diseases. Similar to all medications, this drug also has adverse effects. Even though research on the safety of this drug is limited, its association with malignancy was suspected. However, following an investigation, Sivaraman et al. showed the incidence and rate of overall and site-specific malignancies to be similar in tofacitinib users when compared to the general population [6].

Tofacitinib is commonly prescribed either in a 5-mg or in a 10-mg dosage twice daily depending upon the severity of the disease. However, limited data are available based on the safety of 10 mg tofacitinib as compared to the 5-mg dosage. Is 10 mg tofacitinib twice daily safe to use or is it associated with disastrous consequences when compared to the 5-mg dosage twice daily? This is the main question that should be raised at this particular point.

In order to provide an answer to this important question, we aimed to systematically compare the adverse drug events observed with 5 mg versus 10 mg tofacitinib twice daily for the treatment of autoimmune diseases.

Methods

Searched databases and searched strategies

MEDLINE, EMBASE, the Cochrane library, and www.ClinicalTrials.gov were searched (from March to April 2018) for suitable English publications (published before April 2018) based on the following searched terms:

1. Janus kinase inhibitor and autoimmune diseases or disorders
2. Janus kinase inhibitor and rheumatoid arthritis
3. Janus kinase inhibitor and psoriasis
4. Tofacitinib and autoimmune diseases or disorders
5. Tofacitinib and rheumatoid arthritis
6. Tofacitinib and psoriasis

The PRISMA reporting guideline was followed [7].

Inclusion and exclusion criteria

The inclusion criteria were as follows:

1. Randomized controlled trials (English)
2. Based on patients with autoimmune diseases
3. Compared adverse drug events associated with 5 mg versus 10 mg tofacitinib

The criteria for exclusion were:

1. Non-randomized controlled trials
2. Not based on patients with autoimmune diseases
3. Did not report adverse drug events associated with 5 mg versus 10 mg tofacitinib
4. Consisted of another Janus kinase inhibitor
5. Duplicated studies

Types of participants

Patients with the following health conditions were included in this analysis (Table 1):

1. Rheumatic arthritis
2. Psoriatic arthritis
3. Moderate to severe psoriasis
4. Ankylosing spondylitis

Endpoints and follow-up periods

The following endpoints were assessed (Table 1):

1. Total adverse events
2. Serious adverse events
3. Serious infection events
4. Discontinuation of drug due to adverse events
5. Adjudicated herpes zoster infection
6. Adjudicated opportunistic infections
7. Malignancies
8. Adjudicated major adverse cardiovascular events
9. Decreased hemoglobin levels (anemia)
10. Mild and severe neutropenia

Follow-up time periods of 3 months and ≥ 6 months were considered relevant to this review article.

Data extraction and quality assessment

Two independent reviewers (Feng Huang and Zu-chun Luo) independently extracted data for this review. The following data were extracted: type of study and participants, methodological features of each trial, the total number of participants who were treated with 5 mg and 10 mg tofacitinib, the baseline features of the participants, the adverse drug events which were reported, and the follow-up time periods.

Any disagreement that followed was resolved by consensus.

The bias risk of the trials was assessed with reference to the criteria suggested by the Cochrane Collaboration [15]. A grade "A to C" was allotted based on the methodological qualities of the trials. Grade "A" signified a low risk of bias whereas a grade "C" represented a high risk of bias. Grade "B" represented a moderate risk of bias.

Statistical analysis

Statistical analysis was carried out by RevMan 5.3 (latest version) whereby risk ratios (RRs) with 95% confidence intervals (CIs) were generated.

Heterogeneity was assessed by:

1. The Q statistic test ($P \leq 0.05$ was considered as statistically significant)
2. The I^2 statistic test (the higher the I^2 value, the larger the heterogeneity)

A fixed effects model ($I^2 < 50\%$) or a random effects model ($I^2 > 50\%$) was used based on the I^2 value obtained.

Sensitivity analysis was also carried out to know if the results were consistent across all the trials.

Funnel plots were generated to represent publication bias.

Table 1 Endpoints which were reported in each trial

Trials	Disease being treated for	Endpoints reported	Follow-up period	Dosage of tofacitinib
Fleischmann 2012 [8]	Rheumatoid arthritis	Patients with AEs, patients with serious AEs, serious infection events, discontinuation of drug due to AEs, mild, moderate, severe, life-threatening neutropenia, decreased hemoglobin level	3 months, 3–6 months, 6 months	5 versus 10 mg BD
Gladman 2017 [9]	Psoriatic arthritis	Patients with AEs, patients with serious AEs, serious infection events, discontinuation of drug due to AEs, herpes zoster infection, adjudicated opportunistic infection, adjudicated major adverse cardiovascular events	3 months, 6 months	5 versus 10 mg BD
Mease 2017 [10]	Psoriatic arthritis	Patients with AEs, patients with serious AEs, serious infection events, discontinuation of drug due to AEs, herpes zoster infection, adjudicated opportunistic infection, adjudicated major adverse cardiovascular events, malignancies	3 months, 12 months	5 versus 10 mg BD
van der Heijde 2016 [16]	Ankylosing spondylitis	Patients with AEs, patients with serious AEs, discontinuation of drug due to AEs	3 months	5 versus 10 mg BD
Papp 2016 [11]	Moderate to severe psoriasis	Patients with AEs, patients with serious AEs, discontinuation of drug due to AEs, serious infection events, opportunistic infections, malignancies, herpes zoster infections, major adverse cardiovascular events	12 months	5 versus 10 mg BD
Vollenhoven 2012 [12]	Rheumatoid arthritis	Patients with AEs, patients with serious AEs, serious infection events, discontinuation of drug due to AEs, mild, moderate to severe neutropenia, decreased hemoglobin level	3 months, 3–6 months	5 versus 10 mg BD
Burmester 2013 [13]	Rheumatoid arthritis	Patients with AEs, patients with serious AEs, serious infection events, discontinuation of drug due to AEs, mild and moderate to severe neutropenia	3 months and 6 months	5 versus 10 mg BD
Kremer 2013 [14]	Rheumatoid arthritis	Patients with AEs, patients with serious AEs, discontinuation of drug due to AEs	12 months	5 versus 10 mg BD

AEs adverse events, *BD* twice daily

This table lists the endpoints, the follow-up time periods, and the dosage of tofacitinib which were reported in the original trials

Ethical approval

Ethical or board review approval was not required for this type of study.

Results

Searched outcomes

Searched databases resulted in a total number of 976 publications. This searched result is presented in Table 2. After an initial assessment of the titles and abstracts, 899 publications were eliminated since they were outside the scope of this research topic. Seventy-seven full-text articles were assessed for eligibility.

Further eliminations were carried out based on the following:

- Non-randomized trials including reviews, case reports, and letters to editors ($n = 16$)
- Duplicated studies ($n = 16$)
- Was not based on tofacitinib but involved other JAK inhibitors ($n = 15$)
- Did not report adverse drug events ($n = 8$)
- Did not compare 5 mg versus 10 mg tofacitinib ($n = 14$)

Finally, only eight trials [8–13, 16] were included in this review as shown in Fig. 1.

General features of the trials

A total number of 4287 participants were included (2144 participants received 5 mg tofacitinib and 2143 participants received 10 mg tofacitinib twice daily) as shown in Table 3. The type of study and the bias assessment grade are also listed in Table 3. All the studies were randomized controlled trials. Five trials were allotted a bias risk grade "A" whereas three trials were allotted a bias risk grade "B."

Baseline features of the participants

Baseline features of the participants are listed in Table 4. The mean age varied from 41.2 to 55.4 years. Mean duration of disease ranged from 1.5 to 13.0 years as shown in Table 4. Other features such as the percentage of female participants, the number of participants with increased C-reactive protein (CRP), and increased erythrocyte sedimentation rate (ESR) are also listed in Table 4. According to the baseline features, there was no significant difference in patients who were treated with 5 mg versus 10 mg tofacitinib twice daily.

Adverse drug events associated with 5 mg versus 10 mg tofacitinib twice daily at a 3-month follow-up time period

Our results (Table 5) showed that at 3 months, similar risks of adverse drug events, serious adverse events, and adverse events which lead to drug discontinuation were observed with 5 mg versus 10 mg tofacitinib twice daily for the treatment of autoimmune diseases (RR 1.04, 95% CI 0.98–1.10; $P = 0.17$; RR 1.06, 95% CI 0.77–1.48; $P = 0.71$; and RR 1.06, 95% CI 0.78–1.43; $P = 0.73$, respectively, as shown in Fig. 2). The other outcomes—serious infection events, adjudicated herpes zoster infection, adjudicated opportunistic infection, mild and severe neutropenia, malignancies, and adjudicated major adverse cardiovascular events—were also similarly manifested (RR 1.74, 95% CI 0.93–3.27; $P = 0.09$; RR 1.53, 95% CI 0.68–3.46; $P = 0.30$; RR 0.27, 95% CI 0.05–1.66; $P = 0.16$; RR 1.01, 95% CI 0.47–2.16; $P = 0.98$; RR 1.52, 95% CI 0.43–5.33; $P = 0.52$; RR 0.46, 95% CI 0.16–1.31; $P = 0.15$; and RR

Table 2 Searched results showing the total number of studies which were retrieved from the searched databases

Searched terms	MEDLINE	EMBASE	Cochrane database	www.ClinicalTrials.gov
Janus kinase inhibitor and autoimmune diseases/disorders	348	289	103	65
Janus kinase inhibitor and rheumatoid arthritis	396	365	118	91
Janus kinase inhibitor and psoriasis	301	92	18	21
Tofacitinib and autoimmune diseases/disorders	189	156	75	34
Tofacitinib and rheumatoid arthritis	378	305	122	54
Tofacitinib and psoriasis	45	42	23	20
Total no. of studies (n)	1657	1249	459	285
Total no. of studies after duplicate articles from each database were removed (n)	398	369	118	91

This table shows the total number of publications which were obtained from each electronic database when the respective searched terms were used to identify suitable articles which could possibly be used for this analysis

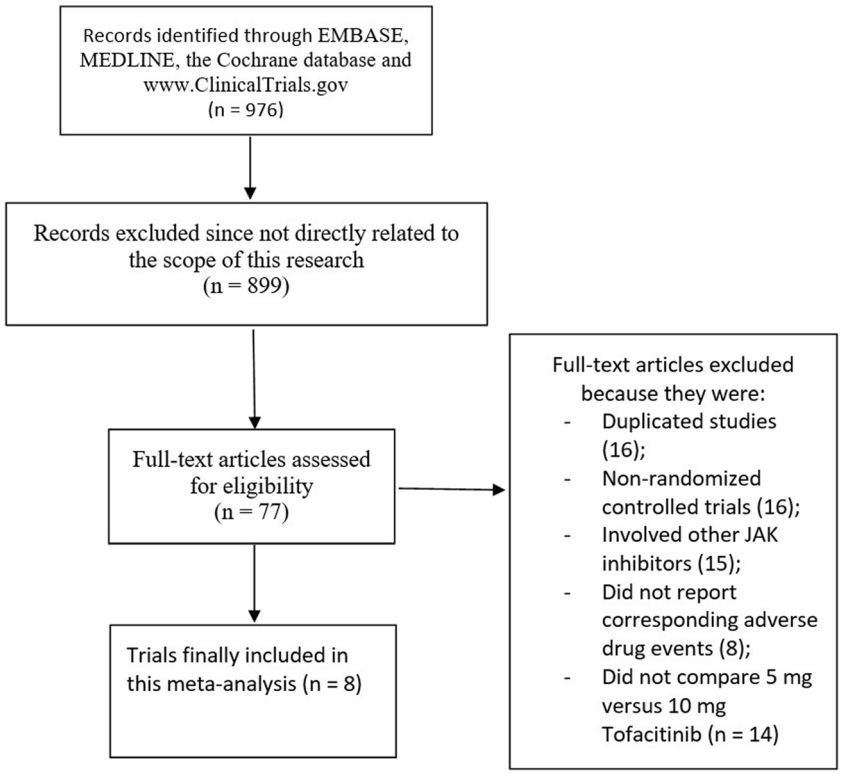

Fig. 1 Flow diagram showing the study selection which was undertaken based on the PRISMA guidelinel

0.67, 95% CI 0.11–3.99; $P = 0.66$, respectively, as shown in Fig. 2).

However, decreased level of hemoglobin (anemia) significantly favored 5 mg tofacitinib (RR 1.75, 95% CI 1.19–2.58; $P = 0.005$) as shown in Fig. 2.

Adverse drug events associated with 5 mg versus 10 mg tofacitinib at a 6-month follow-up time period

At 6 months or more, adverse drug events, serious adverse events, adverse drug events leading to drug discontinuation, and serious infection events were still similarly observed (RR 1.03, 95% CI 1.00–1.07; $P = 0.09$; RR 1.01, 95% CI 0.79–1.30; $P = 0.94$; RR 1.26, 95% CI 0.98–1.62; $P = 0.07$; and RR 1.54, 95% CI 0.89–2.68; $P = 0.12$, respectively as shown in Fig. 3).

Sensitivity analysis and publication bias

When each study was excluded one by one and a new analysis was carried out each time and then compared with the main result, consistent results were obtained each time; that is, sensitivity analysis resulted in consistent results throughout.

Table 3 General features of the trials

Trials	No of patients treated with 5 mg tofacitinib (*n*)	No. of patients treated with 10 mg tofacitinib (*n*)	Type of study	Bias risk grade
Fleischmann [8]	243	245	RCT	A
Gladman [9]	131	132	RCT	A
Mease [10]	107	104	RCT	A
Heijde 2016	52	52	RCT	B
Papp [11]	886	884	RCT	B
Vollenhoven [12]	204	201	RCT	A
Burmester [13]	133	134	RCT	A
Kremer [14]	388	391	RCT	B
Total no. of patients (*n*)	2144	2143		

RCT randomized controlled trials

This table shows the total number of patients which were extracted from each trial, the type of study and the bias risk grades which were assigned based on the recommendation from the Cochrane Collaboration

Table 4 Baseline features of the participants

Trials	Mean age 5 mg/10 mg	Females 5 mg/10 mg	CRP 5 mg/10 mg	ESR 5 mg/10 mg	Duration of disease 5 mg/10 mg	Other medication which were used
Fleischmann [8]	52.2/52.4	85.2/88.2	22.9/19.1	53.1/52.1	8.0/8.6	Tofacitinib monotherapy
Gladman [9]	49.5/51.3	64.0/74.0	85.0/82.0	–	9.6/9.1	Tofacitinib following inadequate response to TNF inhibitors
Mease [10]	49.4/46.9	53.0/60.0	64.0/63.0	–	7.3/5.4	Tofacitinib following inadequate response to conventional synthetic DMARDS
Heijde 2016	41.2/41.6	25.0/26.9	67.3/65.4	–	3.5/1.5	Tofacitinib monotherapy
Papp [11]	46.0/45.0	29.0/30.1	–	–	–	Tofacitinib monotherapy
Vollenhoven [12]	53.0/52.9	85.3/83.6	14.9/19.3	48.6/49.9	7.6/7.4	Tofacitinib following methotrexate treatment
Burmester [13]	55.4/55.1	85.0/86.6	–	26.1/22.9	13.0/12.6	Tofacitinib following inadequate response to TNF inhibitors
Kremer [14]	52.7/51.9	83.8/81.1	–	28.7/28.5	8.1/9.2	Tofacitinib in combination with synthetic DMARDS

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *TNF* tumor necrosis factor, *DMARDS* disease-modifying anti-rheumatic drugs

Mean age and mean duration of disease were reported in years. The other features were reported as percentage. This table lists the baseline features of the participants as well as any other medications which were being used by the participants to treat their current autoimmune disorders

In addition, there was low evidence of publication bias across all the trials that assessed adverse drug events as shown in Figs. 4 and 5. It should be noted that due to a small volume of studies which were included in this meta-analysis, the best way to assess publication bias was through the RevMan generated funnel plots.

Discussion

In this study, adverse drug events which were observed with 5 mg versus 10 mg tofacitinib twice daily were assessed. The current results showed no significant difference in adverse drug events between the two dosages of tofacitinib. Both

Table 5 Results of this analysis

Endpoints assessed	RR with 95% CI	*P* value	I^2 value (%)
3-month outcomes			
Patients with AEs	1.04 [0.98–1.10]	0.17	0
Patients with serious AEs	1.06 [0.77–1.48]	0.71	0
Discontinuation of drugs due to AEs	1.06 [0.78–1.43]	0.73	32
Serious infection events	1.74 [0.93–3.27]	0.09	0
Adjudicated opportunistic infection	1.53 [0.68–3.46]	0.30	0
Adjudicated opportunistic infection	0.27 [0.05–1.66]	0.16	0
Mild neutropenia	1.01 [0.47–2.16]	0.98	0
Moderate to severe neutropenia	1.52 [0.43–5.33]	0.52	0
Decreased hemoglobin level	1.75 [1.19–2.58]	0.005	49
Malignancies	0.46 [0.16–1.31]	0.15	0
Adjudicated major adverse cardiovascular events	0.67 [0.11–3.99]	0.66	–
6 months or more			
Patients with AEs	1.03 [1.00–1.07]	0.09	16
Patients with serious AEs	1.01 [0.79–1.30]	0.94	0
Discontinuation of drugs due to AEs	1.26 [0.98–1.62]	0.07	17
Serious infection events	1.54 [0.89–2.68]	0.12	0

RR risk ratios, *CI* confidence intervals, *AEs* adverse events

This table summarizes the main results of this analysis, listing the respective risk ratios and the corresponding confidence interval as well as the *P* value and the I^2 value

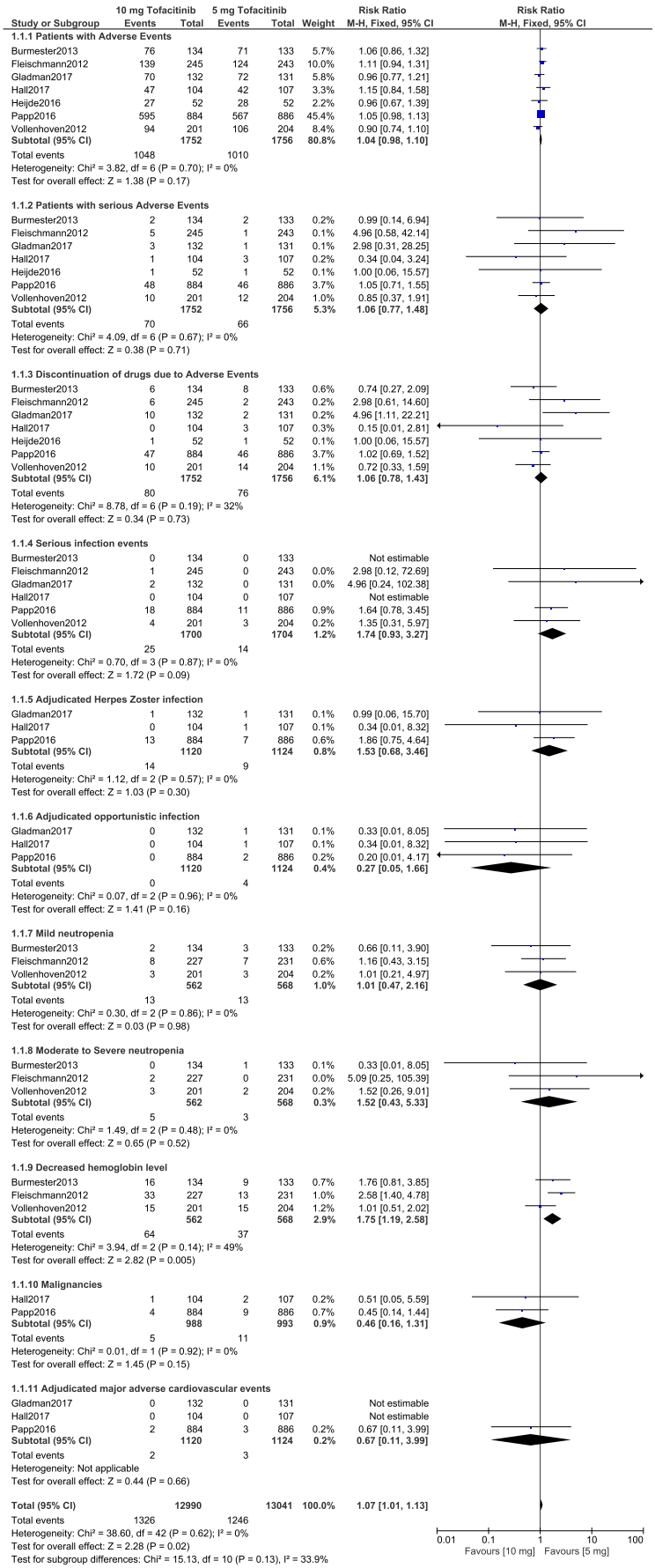

Fig. 2 Adverse drug events which were observed with 5 mg versus 10 mg tofacitinib twice daily during a follow-up time period of 3 months

dosages (5 mg and 10 mg) were equally tolerable. Malignancies and infections were also similarly observed with 5 mg and 10 mg tofacitinib respectively. However, anemia (decreased hemoglobin level) was significantly higher with 10 mg tofacitinib at a follow-up time period of 3 months. It should be noted that a longer follow-up time period for anemia was not reported in the original trials.

Efficacy of tofacitinib was previously shown in a meta-analysis whereby tofacitinib represented a statistically significant improvement in outcomes according to the response criteria (ACR20/50/70) [17]. Several phase II trials have also shown tofacitinib to be effective in those patients with rheumatoid arthritis who did not respond to disease-modifying anti-rheumatic drugs (DMARDs) [8, 12].

Adalimumab is a biologic agent which is often used for the treatment of autoimmune disorders. Recent studies have shown adalimumab monotherapy or in combination with methotrexate not to be superior to tofacitinib indicating that the latter has some potential benefit in these patients with autoimmune disorders [18]. Tofacitinib has shown to be beneficial in most of the patients with multiple failed biologics [8], and because of the several potential advantages, it has recently been recommended in the USA for the treatment of rheumatoid arthritis.

Oral tofacitinib is already being used for the treatment of psoriasis, another autoimmune disease [19]. In dermatology, corticosteroids have often been used as topical agents for skin disorders. However, long-term use of topical corticosteroids might result in skin atrophy and telangiectasia. Topical applications of tofacitinib are now being considered [20] and this might even replace corticosteroids in the near future.

Furthermore, the ORAL Start study showed that tofacitinib could reduce the sign and symptoms of rheumatoid arthritis and improve physical functioning when compared to

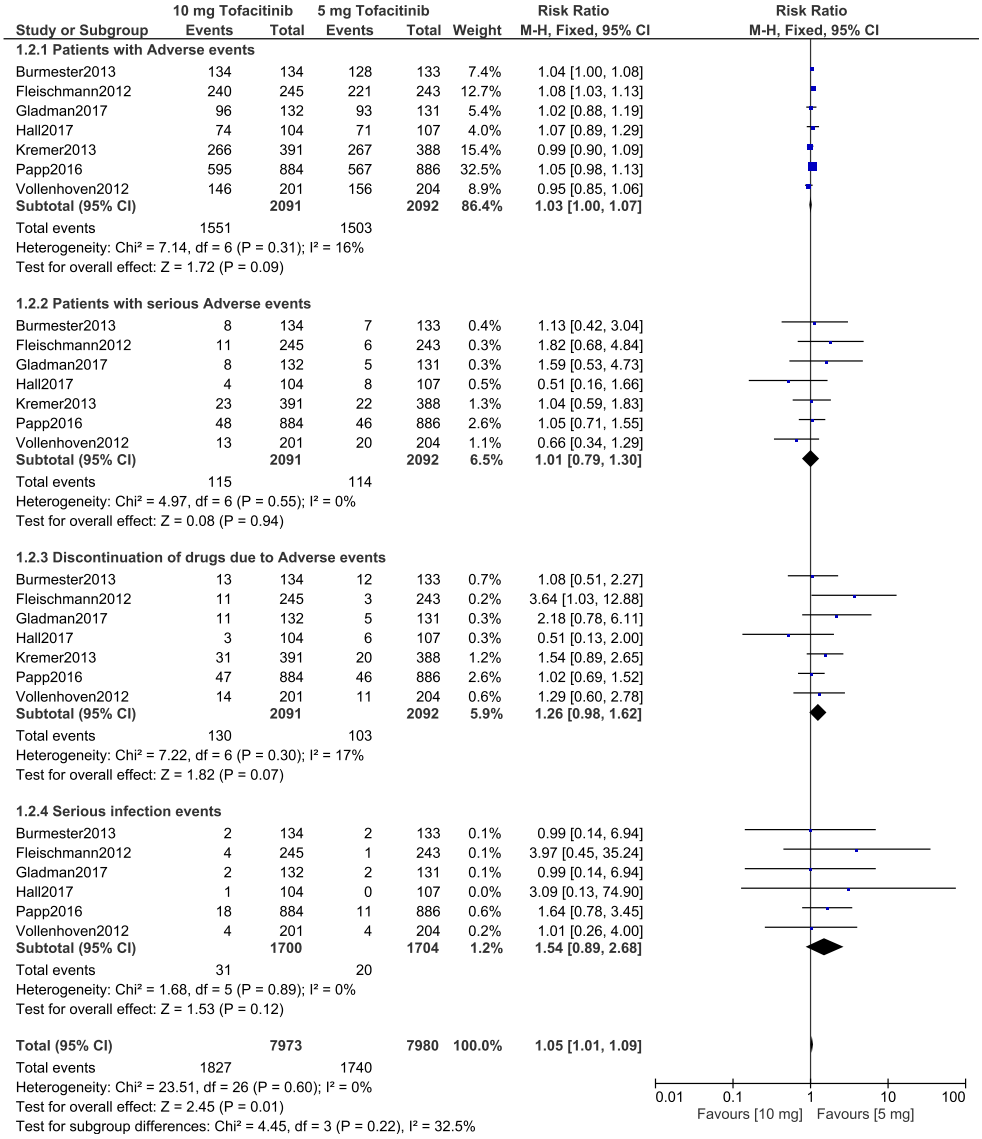

Fig. 3 Adverse drug events which were observed with 5 mg versus 10 mg tofacitinib twice daily during a follow-up time period of ≥ 6 months

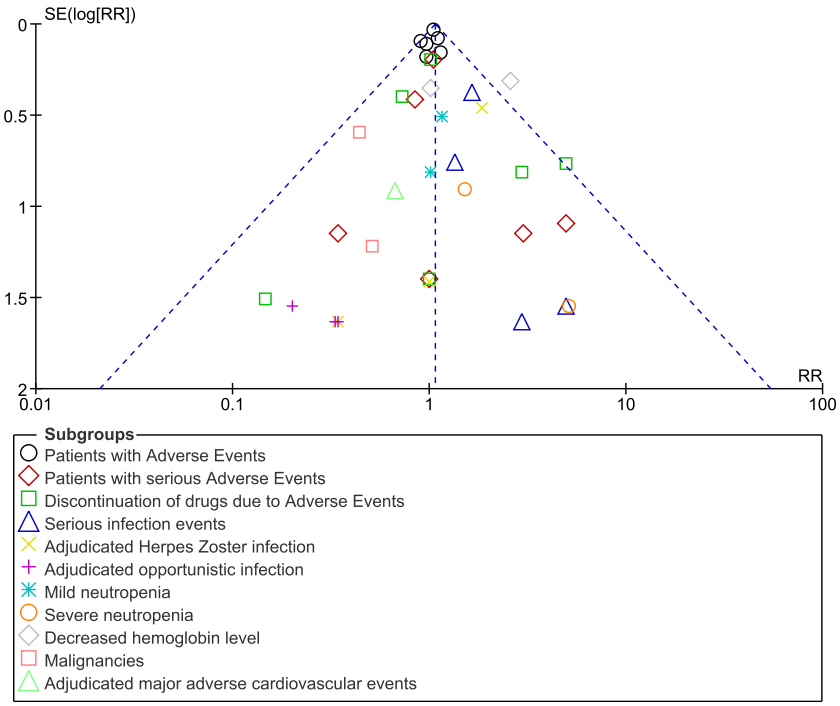

Fig. 4 Funnel plot representing publication bias. A low publication bias was observed across all the trials that assessed the adverse drug events

methotrexate [21]. However, treatment should be started at an early stage of the disease [22], where a dosage of tofacitinib 5 mg would be sufficiently enough to significantly reduce these signs and symptoms.

Oral tofacitinib 5 mg twice daily is approved for use alone or in combination to DMARDS [23]. A significantly higher number of patients who were treated with either 5 mg or 10 mg tofacitinib two times a day could achieve at least a 20% improvement in ACR criteria (ACR20) following 3 months of treatment in comparison to placebo as shown in the ORAL Solo study [8]. It should be noted that the participants who were enrolled in the ORAL Solo study did not have an adequate response to at least one non-biologic DMARD at baseline.

This current review showed similar adverse events with both drug dosages. Even the results of two phase 2 randomized controlled trials showed similar risk of adverse events in patients who were treated with 5 mg versus 10 mg tofacitinib further supporting this current analysis [24] followed by another recent review [25]. An integrated analysis of data from

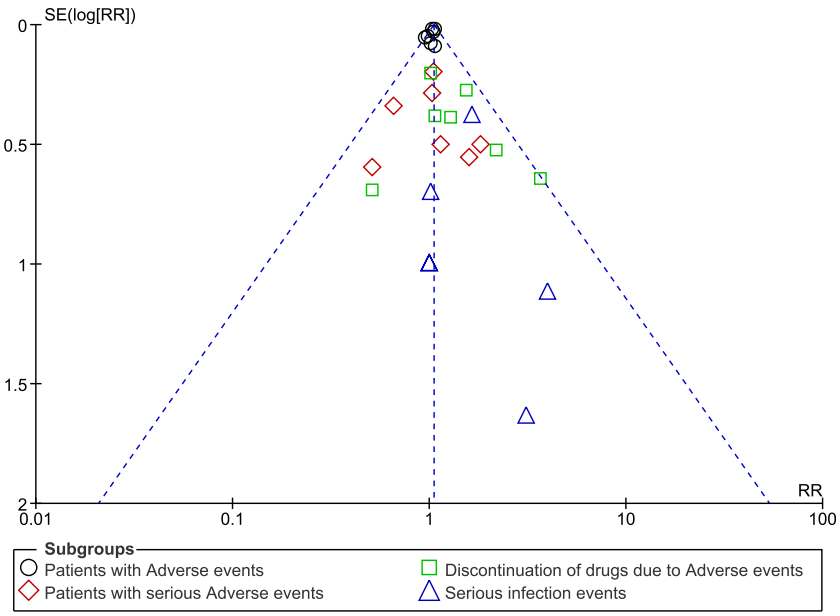

Fig. 5 Funnel plot representing publication bias. A low publication bias was observed across all the trials that assessed the adverse drug events

the global clinical trials whereby 6194 patients received tofacitinib for a total 19,406 patient-years' exposure of up to 8.5 years allowed estimation of safety outcomes with improved precision and demonstrated adverse drug events to be generally stable over time [26].

In contrast, a recent cohort study (comprising of 21,832 participants with rheumatoid arthritis) which involved the MarketScan databases (2011–2014) to study methotrexate-exposed patients with rheumatoid arthritis who were newly prescribed tofacitinib, DMARDs other than methotrexate, and biologics showed that the comparison of tofacitinib with non-TNF biologics did not demonstrate any significant difference with respect to efficacy of treatment [27].

This current review showed anemia to be more prominent with the use of tofacitinib 10 mg at a 3-month follow-up time period. Another study analyzing the hematological changes in tofacitinib-treated patients with rheumatoid arthritis partially supported our results and showed clinically meaningful decrease in hemoglobin levels which occurred in less than 1% of the patients in all treatment groups [28] and the authors stated that this mild deviation in blood parameters would finally settle over time. Other studies have also demonstrated tofacitinib-related anemia [29, 30]. Nevertheless, no association of tofacitinib with anemia was shown in a recent review article [31]. Unfortunately, we do not have any explanation for this association of high-dose tofacitinib with anemia at present and, in this current study, data was not available to compare anemia at a 6-month follow-up.

Research on the safety outcomes of tofacitinib in the treatment of autoimmune diseases is new hence limited. In this analysis, all the published trials which assessed safety outcomes in terms of adverse drug events were systematically analyzed to reach a generalized conclusion, which might be as important clinically.

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway has interested research scientists for years and now new drugs have been, and are still being, introduced for the treatment and management of several autoimmune diseases such as rheumatoid arthritis and psoriasis [2]. The mechanisms have previously been described [2]. This JAK-STAT signaling pathway has a major role dealing with cytokines, cellular immune response, and antibody-mediated response as well as in inflammatory disorders.

Tofacitinib and baricitinib have been approved for the treatment of some autoimmune disorders due to their successful inhibition of enzymatic activities while other immune-related disorders will also benefit from this class of drug in the near future [32].

Even if a number of JAK inhibitors such as filgotinib, peficitinib, ABT-494, and decernotinib are currently undergoing testing in clinical trials, forthcoming research should now focus on the long-term outcomes, and whether risk of different types of malignancies and infections is associated with these JAK inhibitors.

Novelty

- This review assesses an important issue in clinical rheumatology, an important idea concerning dosage therapy and adverse drug effects associated with tofacitinib for the treatment of autoimmune diseases.
- This study is interesting and useful and could be used in a real-life setting as suggested by one of the reviewers.
- This analysis is the first one to systematically compare 5 mg versus 10 mg tofacitinib twice daily for the treatment of autoimmune diseases.
- A low level of heterogeneity was observed in almost all the subgroups signifying that good-quality data were used in this review.

Limitations

- Even if the total number of participants were sufficient to reach a conclusion, even more participants would have better represented the review.
- There were a limited number of trials which were included during subgroup analysis.
- Other drugs which were used to treat the autoimmune disease were not taken into consideration and they might have influenced the results.
- In addition, we could not find any specific explanation for the association of anemia with a higher dosage of tofacitinib at a 3-month follow-up time period. No data was available to further compare this outcome at a 6-month follow-up. Therefore, we could not provide an explanation for this tofacitinib-related anemia which we further consider a limitation of this study.

Conclusions

According to this current review, both dosages of tofacitinib were safe to use. Even if similar adverse drug events were observed with 5 mg versus 10 mg tofacitinib twice daily for the treatment of autoimmune disorders, anemia was more prominent with 10 mg tofacitinib at a 3-month follow-up. Nevertheless, future studies based on a larger population size with longer follow-up time periods should further be considered.

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Authors' information Dr. Feng Huang (M.D) is the first author.

Authors' contributions FH and ZL were responsible for the conception and design, acquisition of data, analysis and interpretation of data, and drafting the initial manuscript and revising it critically for important intellectual content. FH wrote and approved the final manuscript.

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Compliance with ethical standards

Disclosures None.

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