Review

Efficacy and safety of down-titration *versus* continuation strategies of biological disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis with low disease activity or in remission: a systematic review and meta-analysis

M. Jiang, F. Ren, Y. Zheng, R. Yan, W. Huang, N. Xia, L. Luo, J. Zhou, L. Tang

Department of Rheumatology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China.

Mei Jiang, MD
Feifeng Ren, MD
Yaning Zheng, MD
Ruyu Yan, PhD
Wenhan Huang, MD
Ning Xia, MD
Lei Luo, MD
Jun Zhou, MD
Lin Tang, PhD

Please address correspondence to:
Dr L. Tang,
Department of Rheumatology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, 400010, China.
E-mail: hopetang@163.com

Received on March 18, 2016; accepted in revised form on July 25, 2016.

Clin Exp Rheumatol 2017; 35: 152-160.

Key words: rheumatoid arthritis, remission, disease-modifying anti-rheumatic drugs, dose reduction, meta-analysis

Competing interests: none declared.

ABSTRACT

Objective. *To evaluate the efficacy and safety of down-titration (dose reduction/tapering) strategies compared with continuation of biological disease-modifying anti-rheumatic drugs (DMARDs) in patients with rheumatoid arthritis (RA) who achieved and maintained low disease activity or remission.*

Methods. *We searched the following electronic database up to March 2016: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and conference proceedings of the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR). Our meta-analysis included randomized controlled trials (RCTs) of RA patients with low disease activity or in remission that compared down-titration treatment with continuation treatment. Data on flare, defined as a 28-joint Disease Activity Score of ≥3.2, had to have been reported. Outcomes on efficacy or safety were collected.*

Results. *Of 1136 references identified, five RCTs (total, 771 participants) were included. The incidence of disease relapse in the down-titration and continuation groups was similar (risk ratio (RR)=1.14, 95% CI=0.88–1.49). There was no statistical difference in the number of serious adverse events (RR=1.15, 95% CI=0.53–2.49). Withdrawals due to inefficacy or toxicity were similar between groups and no clinically meaningful difference in efficacy outcomes was observed by continuation treatment.*

Conclusion. *Our findings indicated that continuing a standard dose of biological DMARDs in patients with low disease activity conveyed no significant benefit as compared with down-titration therapy, suggesting that a down-titration strategy is as effective as a continuation strategy. Since the number of trials meeting the criteria for this meta-analysis was relatively low, future analyses with additional prospective RCTs are required to compare other biological agents and evaluate the long-term efficacy of these two strategies.*

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder associated with progressive destruction to the bone and cartilage of the joints, functional disability, and reduction in health-related quality of life (1, 2). The introduction of biological disease-modifying anti-rheumatic drugs (DMARDs), including TNF-α inhibitors (certolizumab pegol, golimumab, infliximab, etanercept (ETN), and adalimumab (ADA)), as well as some other biologic agents (anakinra, rituximab, abatacept (ABA), and tocilizumab), significantly reduces the signs and symptoms of joint damage and improves physical function and quality of life (3-5). However, the economic burden to the RA patient subsequently increases, and long-term therapy with biologics has been associated with a high risk of dose-dependent adverse effects, including an increased risk of serious adverse events (SAEs), especially infection and malignancy (6, 7). Over the last few decades, coupled with early diagnosis, increasing numbers of RA patients have achieved low disease activity and even sustained remission. In response, patients often inquire whether continuation of biological DMARDs is still necessary or whether

the dose can be reduced or even terminated, while keeping the disease under control, which is a central challenge to rheumatologists. Numerous studies to answer these questions have reported high instances of flaring and deterioration following withdrawal from biological DMARDs, as compared to continuing treatment (8, 9). Moreover, emerging evidence indicates that reducing the dose of ETN was more effective than that of methotrexate (MTX) alone to maintain low disease activity, which implies that reducing the biological DMARD dose might be an interesting alternative to maintain low disease activity (10, 11). Meanwhile, the European League Against Rheumatism (EULAR) guidelines mentioned the possibility of tapering biological DMARDs for patients in sustained remission (12). On the other hand, Kobelt (13) estimated the cost-effectiveness of three maintenance strategies in the PRESERVE study (patients failing to maintain remission on half-dose ETN or MTX alone, switching to a full dose of ETN, and patients maintaining remission on full-dose ETN and allowed to switch to a half dose) and found that the half-ETN strategy was the most beneficial. Therefore, we presumed that low-dose biologics might be sufficient to reduce the incidence of SAEs or relieve the economic burden of RA treatment. Therefore, the objective of this systematic review was to determine whether the doses of biological agents could be reduced for patients with low disease activity.

Materials and methods

Literature search

We performed a search of the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases for relevant articles published up to March 2016. Search terms included specific types of biological DMARDs (*e.g.* ADA and ETN) and the terms "dose reduction", "down-titration", "dose de-escalation", "dose tapering", "interval widening", and "rheumatoid arthritis" (the full search strategy is available in the supplementary data). We also searched the abstracts of the American College of Rheumatology (ACR) from 2012 to 2015 and EULAR from 2002 to 2015. The search was limited to studies in English and supplemented by reviewing the references of all relevant studies. If potentially relevant studies included non-published data, the primary investigators of the relevant studies were contacted.

Study selection

Studies were eligible by meeting the following inclusion criteria: (i) randomised controlled trials (RCTs); (ii) conducted in adult RA patients with a state of low disease activity, defined as a 28-joint Disease Activity Score (DAS28) of ≤3.2, or in remission (DAS28 <2.6); (iii) comparing down-titration with continuation of biologics; and (iv) including data on disease relapse (defined as ≥2 additional DMARD courses of high-dose steroids, returned to full-dose biologics, DAS28 >3.2, DAS28 >3.2 with an increase of >0.6, or increase in DAS28>1.2) with or without one or more of the following pre-specified outcomes: DAS28; C-reactive protein (CRP) level; erythrocyte sedimentation rate (ESR); Health Assessment Questionnaire (HAQ) score; radiographic outcomes; pain visual analogue scale (VAS) score; swollen/tender joint count; ACR20; ACR50; ACR70; number of failures; number of SAEs; and withdrawal due to lack of efficacy or SAEs.

Data extraction

Two authors independently used a data extraction form to extract the following information: general study information (title of the article, first author's last name, authors' institution, year of publication, and year of study), study characteristics (design, eligibility criteria, definition and diagnosis of flare, study duration, random sequence generation, allocation concealment, and blinding), intervention (biological DMARDs, dose reduction/tapering, and the integrity of intervention measure), and major outcomes and results presented as numbers, mean deviations, and standard deviations. Any discrepancy in data extraction was resolved by team discussion.

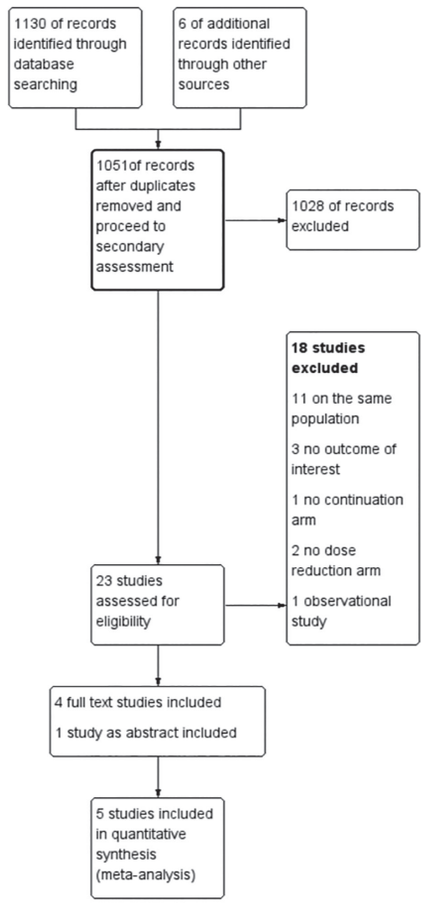

Fig. 1. Search methodology and the literature review process.

Quality assessment

Bias risk of individual studies and across studies was assessed using the Cochrane Collaboration tool (14), according to the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each of the above seven assessed risk of bias domains were evaluated in three groups: A, low risk; B, unclear risk; C, high risk.

Data synthesis

Review Manager 5.3 (http://tech.cochrane.org/revman) was used for all data analyses. The weighted mean difference (WMD) and corresponding 95% confidence intervals (CI) were pooled for analysis using a random-effects model. The WMD was obtained when continuous scales of measurement were used to assess treatment effects (CRP, ESR, VAS, swollen joint count, tender

Table I. Characteristics of studies included for meta-analysis.

Author name (ref. no)	Patient number	Mean patient age (years)	Mean disease duration (years)	Criteria used for treatment initiation	Continuation protocol	Down-titration protocol	Flare definition	Study duration (months)
van Vollenhoven *et al*. (10)	50	56.9	14.3	DAS28 <3.2, [*]LDA >11 months	ETN (50 mg [¥]QW) +MTX	ETN (25 mg QW) + MTX	DAS28 >3.2 or treated with ETN (50 mg weekly)	12
Westhovens et al. (19)	108	50.6	2.3	DAS28 <2.6	ABA (10 mg/kg)	ABA (5 mg/kg)	DAS28 ≥3.2 at two visits, or ≥2 courses of GCS, or additional DMARDs, or treated with ABA (10 mg/kg)	12
Smolen *et al*. (11)	404	47.3	6.6	DAS28 <3.2 for 24 weeks	ETN (50 mg) +MTX weekly	ETN (25 mg) +MTX weekly	DAS28 >3.2 at 52 weeks	12
van Herwaarden *et al*. (15)	180	58.7	10.0	ADA or ETN at any stable dose and interval ≥6 months	Continued ADA of ETN at any stable dose	Step-wise increase in injection interval of every 3 months	DAS28 ≥3.2 with an increase of >0.6, or an increase of DAS28 >1.2	18
Okano *et al*. (20)	29	[#]N.A.	N.A.	DAS28 <3.2	ADA 40 mg every 2 weeks	ADA 40 mg every 4 weeks	DAS28 >3.2	6

[*]LDA: low disease activity, DAS28 <3.2; [¥]QW: once weekly; [#]N.A.: not available.

joint count, HAQ score, and DAS28 mean change from baseline). Categorical data (*e.g*. relapse, ACR20, ACR50, ACR70, number of SAEs, serious infections, and withdrawal because of toxicity or lack of efficacy) were pooled for determination of the risk ratio (RR) and 95% CIs. Statistical heterogeneity was estimated using the χ^2 test and I^2 test, with significant heterogeneity defined as $p<0.1$ and $I^2>50\%$, respectively. Subgroup analyses for different types of interventions (widening injection interval and reduction biologics by 50%) were also performed to explain the heterogeneity.

Results

Study identification

The primary search retrieved a total of 1136 relevant studies. After checking for duplication in EndNote (http://endnote.com/) and reviewing titles and abstracts to exclude clearly irrelevant literature, 23 articles were chosen for secondary evaluation. Six abstracts reported data for the DRESS study. For the purpose of this review, the article by van Herwaarden *et al*. (15) was considered the primary publication, although the abstract by van Vollenhoven *et al*. (10) and three others reported data for the same study. Four abstracts reported data for the STRASS trial, of which we considered the article by Fautrel *et al*. (16) as the primary publication. Additional studies were excluded because eleven of the studies used the same population, three did not report our outcome of interest (16-18), three were not related to dose reduction or continuation strategies, and one was an observational study. Therefore, a total of five RCTs were included in the meta-analysis (four trials compared dose reduction of biological agents with continuation of standard dose and one compared progressively increased

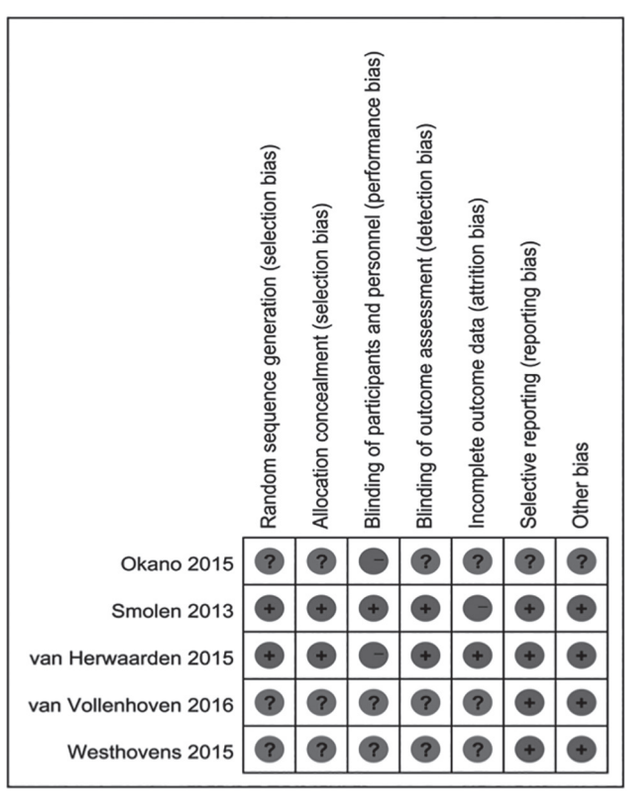

Fig. 2. Risk of bias of the included studies

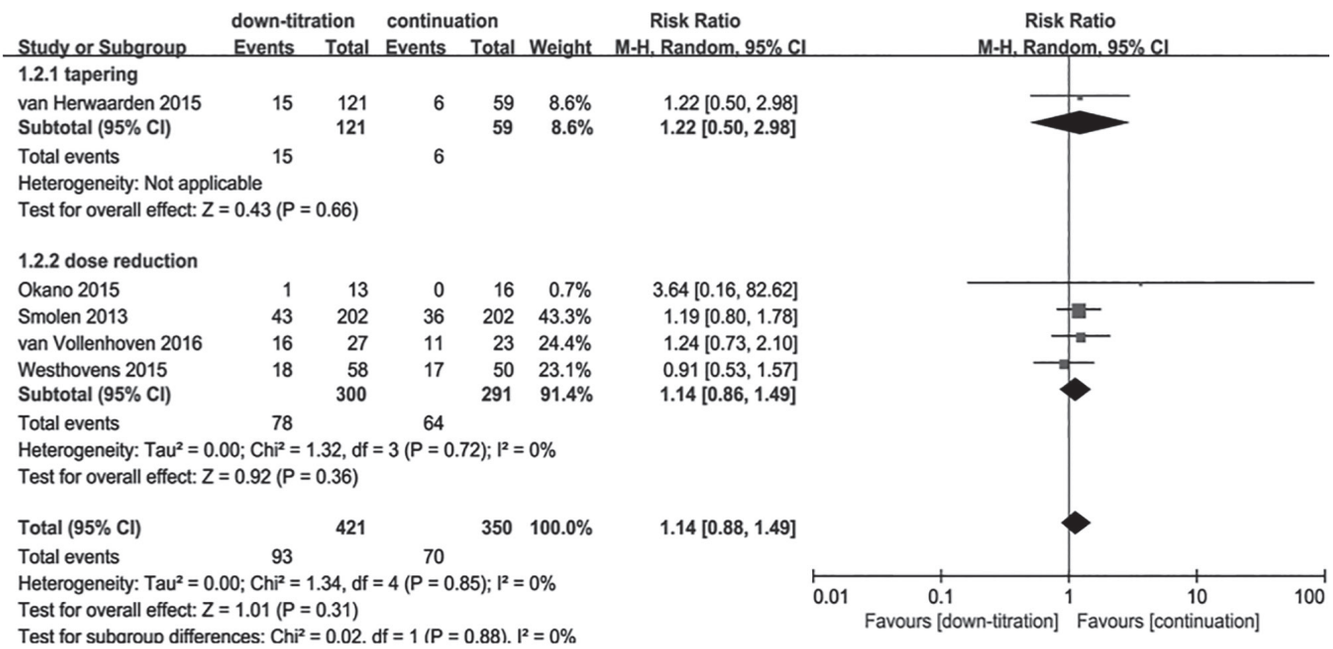

Fig. 3. Proportion of disease relapse in down-titration *versus* continuation therapy.

injection interval with usual care). Figure 1 outlines our literature search and review process.

Characteristics of the included studies

The main characteristics of the included studies are listed in Table I. A total number of 771 participants were included in the trials. Of these, 421 received down-titration therapy and the rest were ascribed to the continuation group. All trials were at least 6 months in duration. Patients in the continuation group received standardised treat-to-target treatment.

Risk of bias of the included studies

The study by Okano *et al*. (20) was only available as conference abstract, and the remaining four trials included in the meta-analysis were published as full text. The PRESERVE trial (11) was judged as high risk of incomplete outcome data, as 13% (>10%) of patients discontinued treatment. The report by van Herwaarden *et al*. (15) met all criteria except for blinding. Two other trials mentioned random sequence generation and were double-blind, but no details were available and they reported a discontinuation rate of 6%–10%. Figure 2 provided the authors' judgements about each risk of bias item for each included study.

Efficacy outcomes

• *Disease relapse*

Data on disease relapse was available for all included studies (771 participants). There was no statistically significant difference in the number of participants who experienced disease relapse between down-titration therapy and continuation therapy (RR = 1.14, 95% CI=0.88–1.49, Fig. 3). The results of the tapering subgroup showed no significant difference in disease relapse by increasing the injection interval and continuation therapy (RR=1.22, 95% CI=0.50–2.98). The dose reduction subgroup showed no difference in reducing biologics by 50% and continuation treatment. Heterogeneity testing revealed no statistically significant difference among the studies (I^2=0%, p=0.85). Excluding the study of widening injection interval did not affect heterogeneity (I^2 =0%, p=0.72).

• *Other efficacy outcomes*

Curative effect indexes (*e.g*. DAS28, CRP, ESR, HAQ score; pain VAS score; swollen/tender joint count, and erosion/joint narrowing score) were reported in three studies and each index was available in one or two. The indexes identified in this meta-analysis are shown in Figure 4. Compared with continuation therapy, functioning change and progression joint space narrowing score were slightly lower by down-titration therapy, but these differences did not reach statistical significance (WMD=0.11, 95% CI=0.03–0.19 and WMD=0.43, 95% CI=0.11–0.74, respectively). Functioning was measured using the HAQ disability index (range, 0–3), with a higher score indicating worse functioning. Radiological progression was assessed according to the modified Sharp/van der Heijde score (range, 0–448) in conjunction with the erosion score (range, 0–280) and joint narrowing score (range, 0–168), where a higher combined score indicates a greater extent of joint damage. There were no statistical differences among the other indexes between groups. ACR and EULAR endpoints were available in only one study (11). No significant difference was observed between the two strategies (Fig. 5).

Safety outcomes

• *Number of SAEs*

All studies except the one reported in the abstract by Okano *et al*. (20) provided data on the incidence of SAEs. The estimated pooled RR is shown in Figure 6. There was no statistically significant difference in outcomes between the down-titration and continuation therapies (RR=1.15, 95% CI=0.53–2.49). The non-significant,

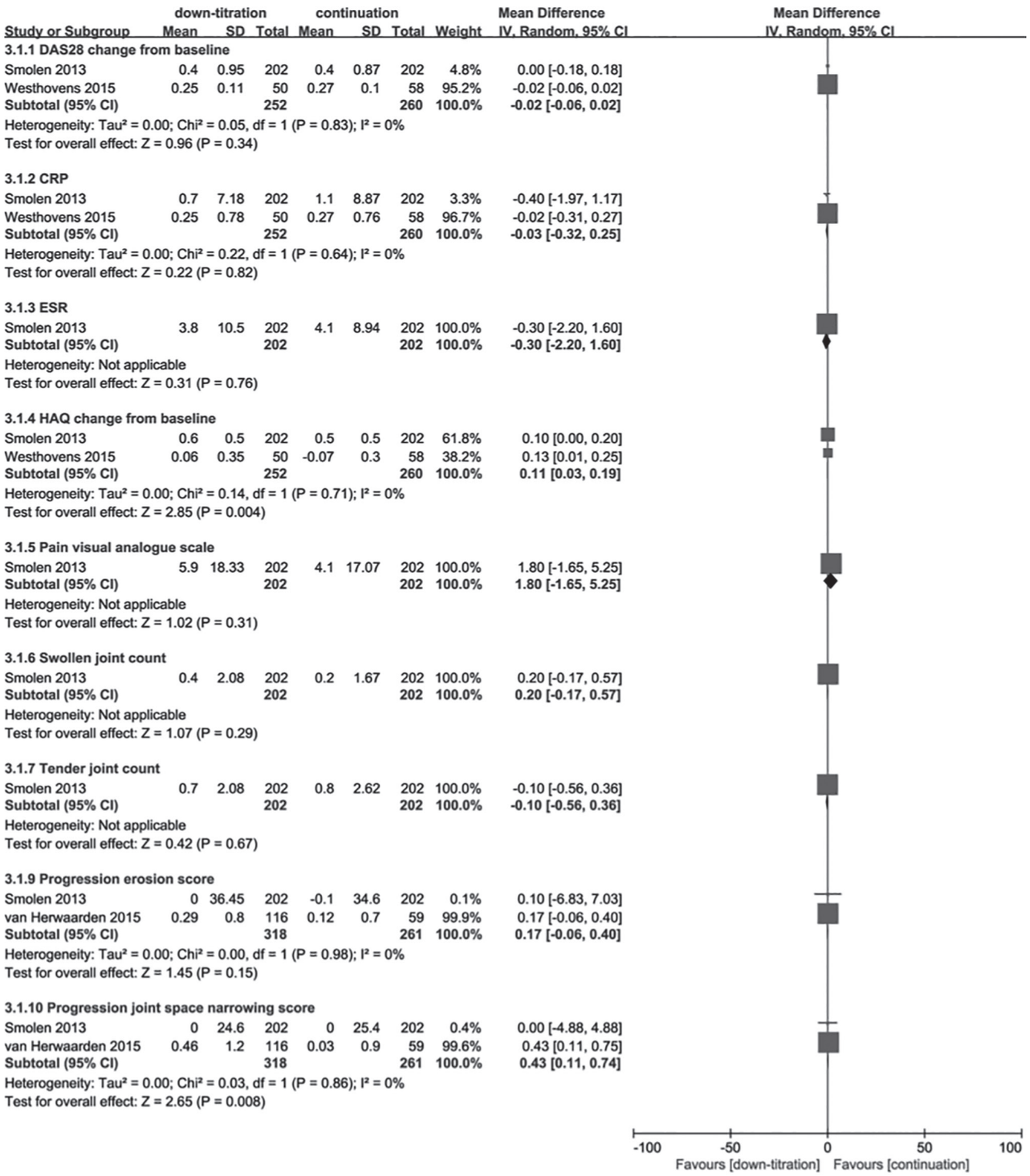

Fig. 4. Clinical indexes in down-titration *versus* continuation therapy.

higher incidence of SAEs in patients receiving widening injection therapy in the DRESS study (15) may caused by a greater acceptance of elective surgery for joint replacement, arthrodesis, and joint prosthesis revision. There is also no significant difference in the incidence of SAEs between the dose reduction and continuation arms. Heterogeneity among studies was not significant (p=0.18, I^2=38%). Excluding the study of widening injection interval showed no significant heterogeneity among the remaining studies (p=0.64, I^2=0%).

• *Number of reported SAEs*

Four full-text studies reported the incidence of at least one SAE (serious infection, allergic reaction, malignancy, cardiovascular event, liver function disorder, or tuberculosis). There was no significant difference in RRs for

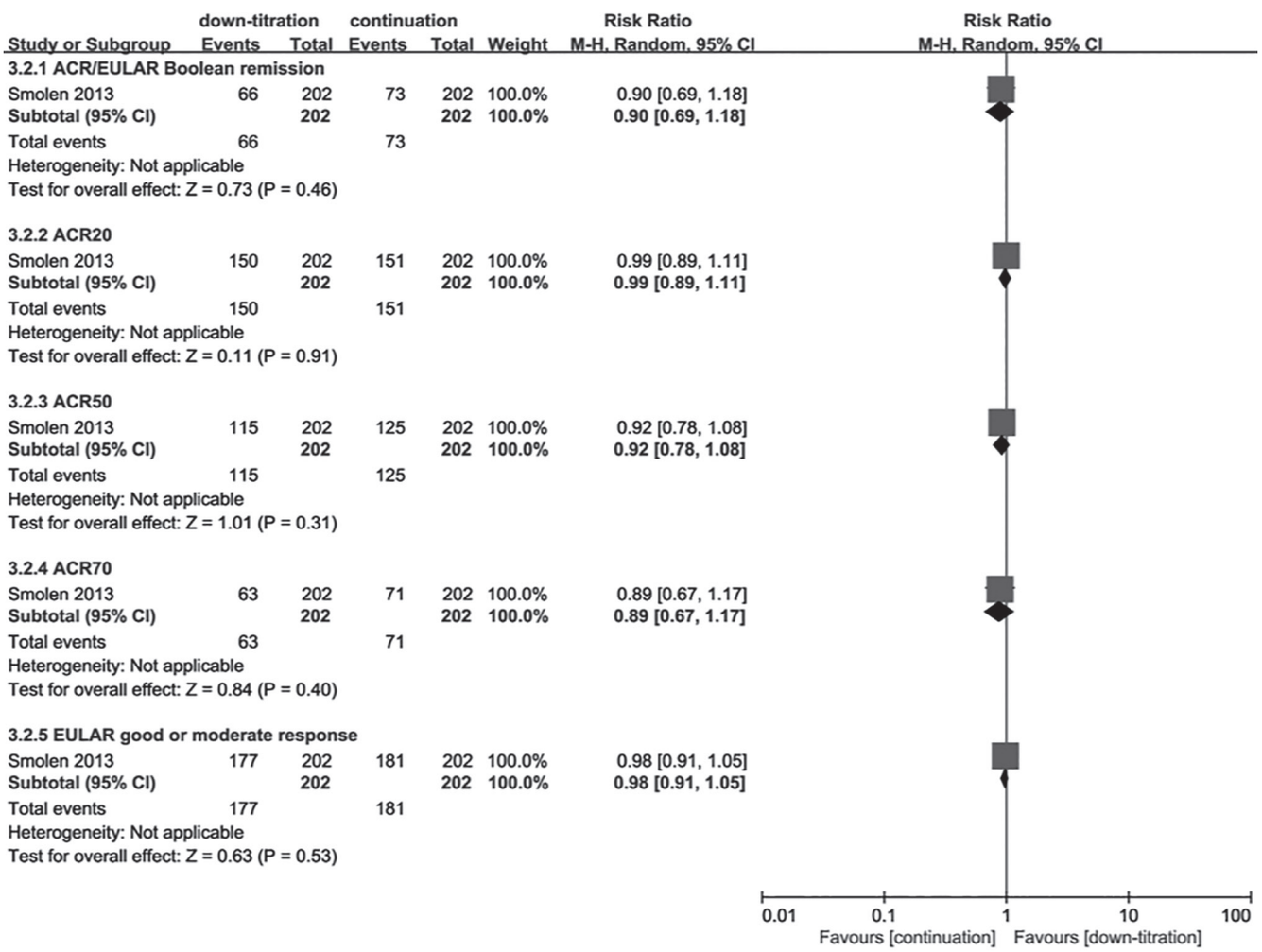

Fig. 5. ACR and EULAR endpoints in down-titration *versus* continuation therapy

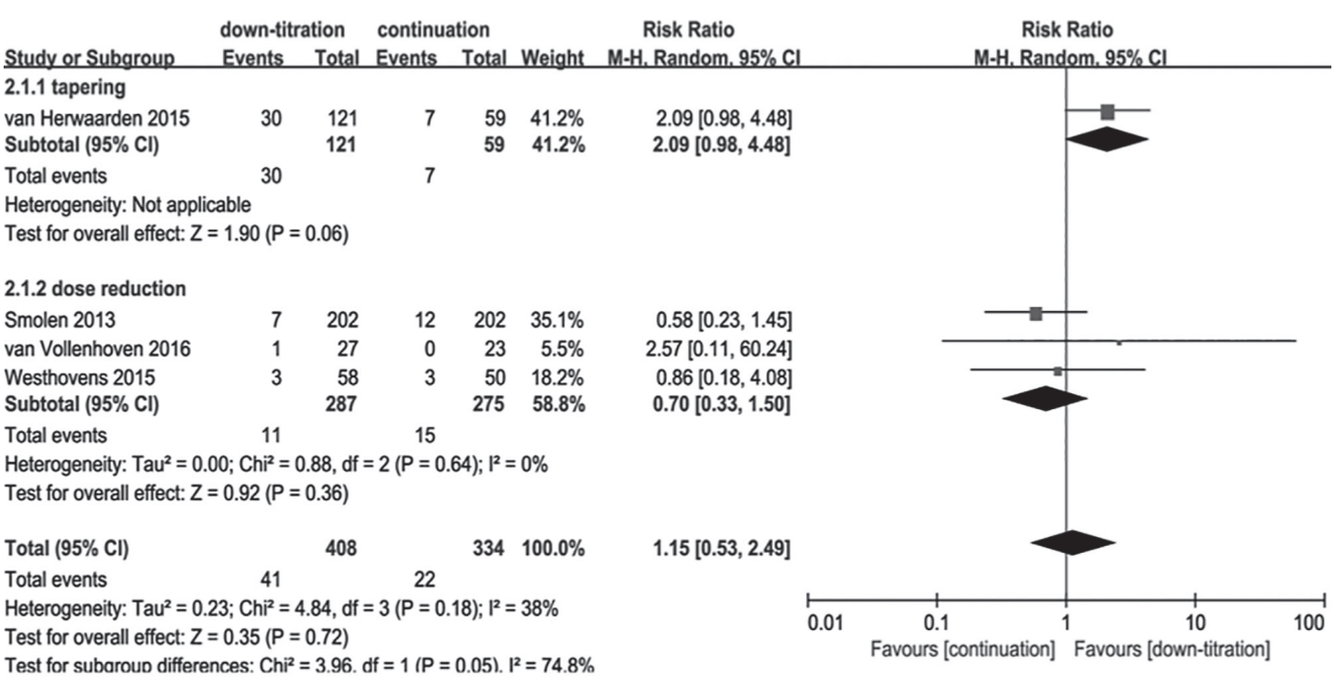

Fig. 6. Number of SAEs in down-titration *versus* continuation therapy.

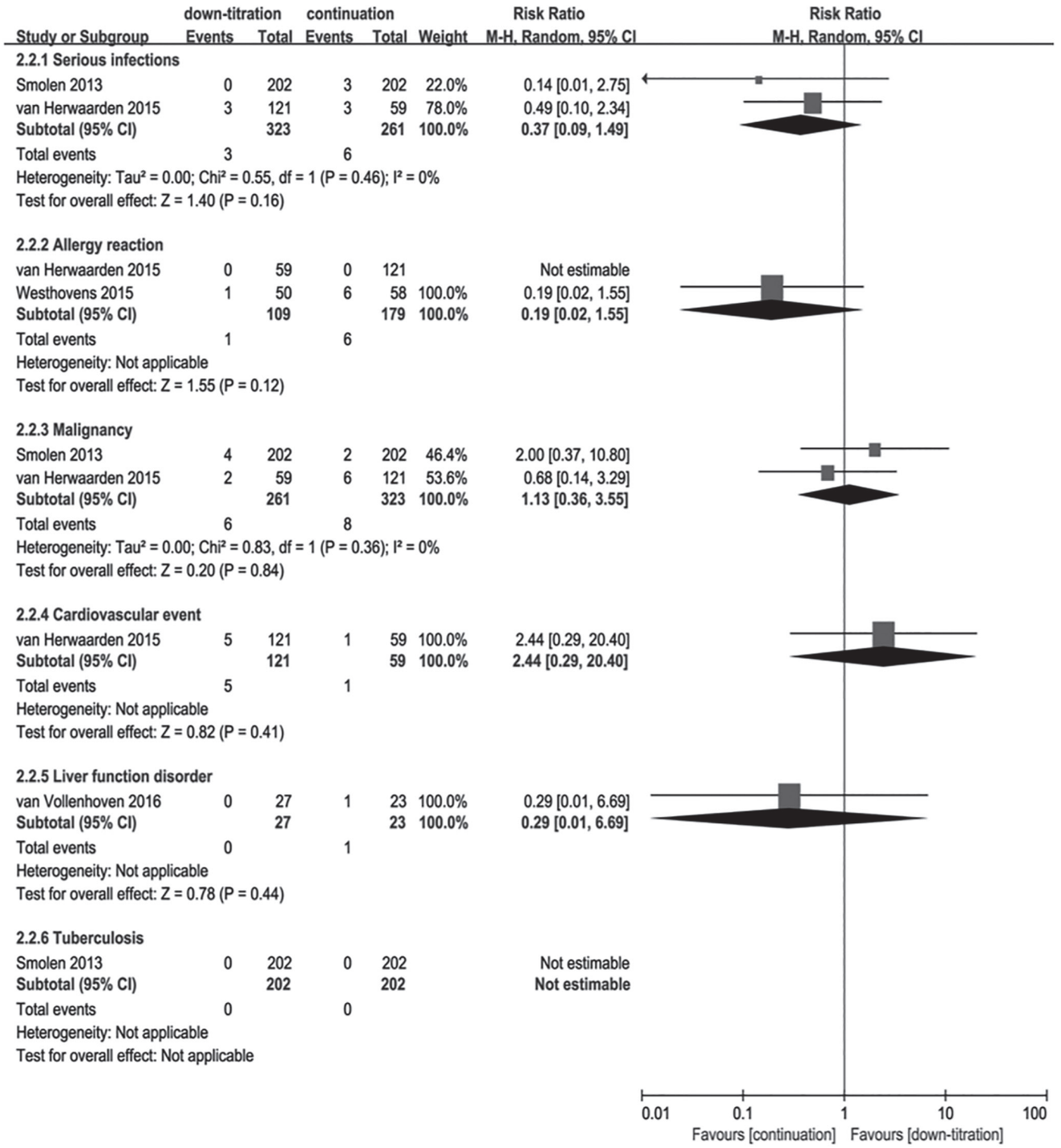

Fig. 7. Incidence of individual SAEs in the down-titration group *versus* continuation group.

each SAE between down-titration therapy and continuation therapy among studies, as shown in Figure 7.

• *Withdrawal because of SAEs or lack of efficacy*

The number of patients who withdrew due to SAEs and lack of efficacy was available in three and two trials, respectively. Down-titration therapy resulted in less patient withdrawal due to SAEs and more patients withdrew due to inefficacy than with continuation therapy, but this difference as not statistically significant (RR=0.80, 95% CI=0.28–2.34 and RR=1.36, 95% CI=0.54–3.44, respectively, Fig. 8A-B). Also, no significant statistical difference was observed in the total number of withdrawals because of SAEs or inefficacy (RR=1.37, 95% CI=0.67–2.77, Fig. 8C).

Discussion

In consideration of both the benefit and potential harm of biological agents, the objective of our systematic review, summarizing evidence from five RCTs,

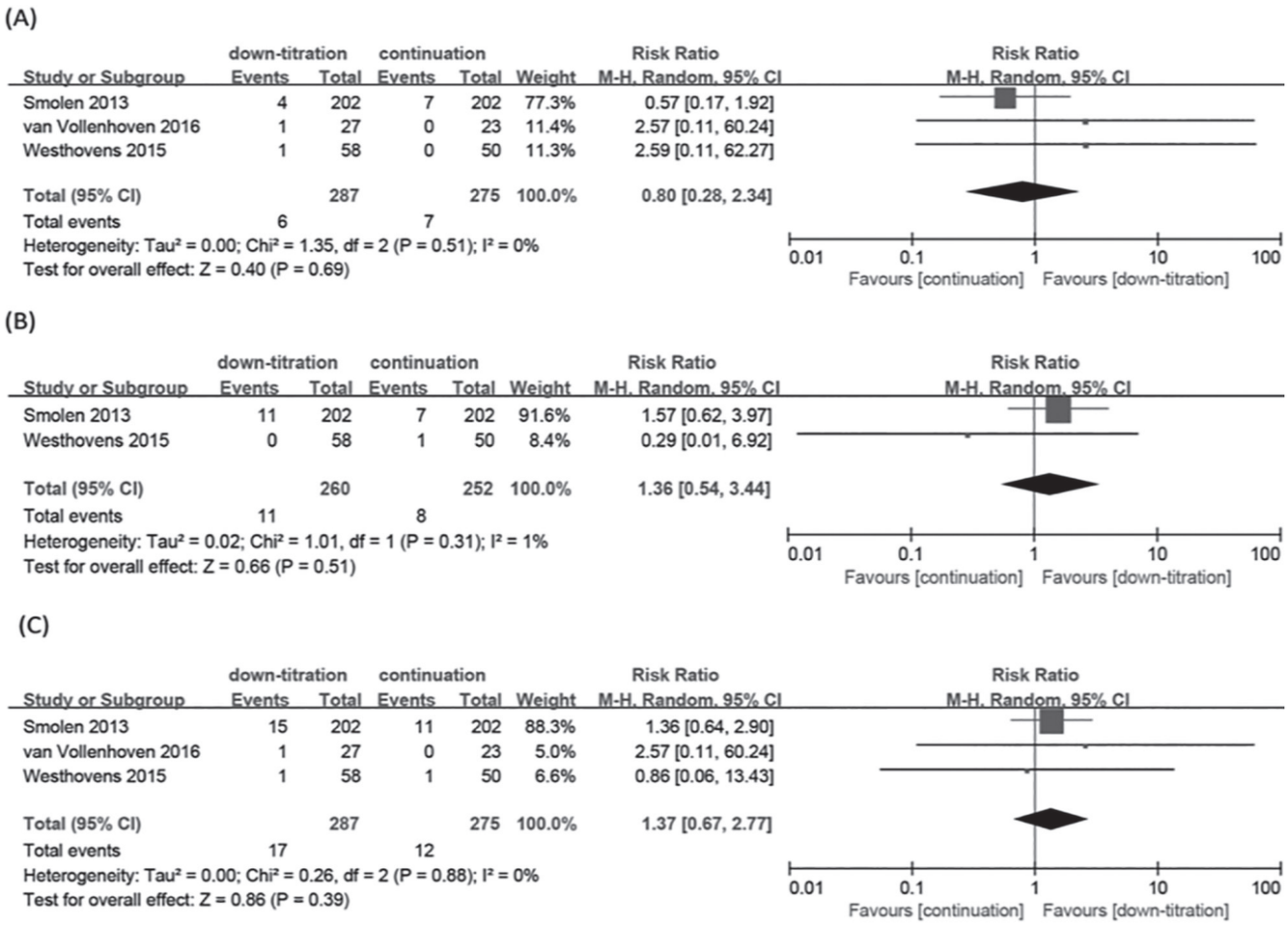

Fig. 8. Withdrawal because of toxicity or inefficacy in the down-titration group *versus* continuation group: (**A**) Withdrawal due to SAEs, p=0.69; heterogeneity: p=0.51, I^2=0%. (**B**) Withdrawal due to lack of efficacy, p=0.51; heterogeneity: p=0.31, I^2=1%. (C) Total withdrawals due to lack of efficacy or SAEs, p=0.88; heterogeneity: p=0.39, I^2=0%.

was to examine whether the dose of biological DMARDs could be reduced in RA patients with low disease activity or in remission. The results of this meta-analysis, involving various drugs, including ETN, ADA, and ABA, demonstrated no significant increase in disease relapse by reduction/tapering therapy as compared with continuation therapy, while continuing biologics conveyed no significant benefit according to clinical indexes.

In regard to safety, the occurrence of overall SAEs or serious infection was similar between down-titration therapy and continuation therapy, although it has been thought to be dose-dependent, which might be explained by "dilution of the susceptible" or "healthy survivor bias" (21). Patients at a higher risk of infection tended to stop DMARDs more quickly after treatment initiation and were less likely to achieve sustained remission with such treatment modifications. The simplest criterion of a benefit/risk ratio for drug evaluation is when a drug is withdrawn because of lack of efficacy or onset of SAEs. Our meta-analysis suggested that the incidence of discontinuation of treatment because of toxicity or inefficacy in down-titration strategies with biologics was the same as with continuation of biologics.

Two observational studies are probably more relevant to address the question of biologics down-titrating. Van der Maas *et al*. (22) was the first team to combine down-titration and discontinuation of biologic treatment (infliximab), but found no relevant deterioration of disease activity in patients with long-standing low disease activity. van Herwaarden *et al*. (23) found that 77% and 55% of patients with low disease activity had successfully reduced the dose of tocilizumab (8 mg/kg at baseline tapered to 4 mg/kg) after 3 and 6 months follow-up, respectively, without compromising disease control (DAS28 >3.2 and/or judgement of the rheumatologist). Three other RCTs, comparing dose reduction treatment with continuation treatment, were not included in our meta-analysis because of differences in the definition of flare (16-18). Nonetheless, these trials reported a higher risk of failing to achieve remission by increasing the interval of injections, reducing dosage, or withdrawal of DMARDs.

Our results provide evidence to a recently published, long-term, follow-up study, where 81.8% patients in the ETN half-dose group maintained remission for about 3.6 years, with no significant difference in the rate of radiographic

progression between the standard-dose group and the half-dose group (18). Two previous systematic reviews compared dose reduction or tapering with continuation therapy (9, 24). Van Herwaarden *et al*. (9) reported that reducing doses of anti-TNF-α therapy was slightly less beneficial than with continuation therapy in regard to the proportion of patients who maintained low disease activity, including RA remission and non-failure. Kuijper *et al*. (24) found that more than one-third of RA patients with low disease activity or in remission may taper or stop biological DMARD treatment without experiencing disease relapse within the first year. However, these findings could not be compared with our study because of the inclusion of half-dose, tapering, and stop strategies.

There were some important limitations to this systematic review that should be addressed. First, the numbers of included studies and drugs were relatively low in this meta-analysis. Second, the inclusion criterion of patients was somewhat overlapped among studies, as one included patients in remission (19) and three included patients with stable low disease activity (10, 11, 15). Nonetheless, this meta-analysis provides useful information that reducing the dosages of biological DMARDs may be a practicable strategy to maintain low disease activity. However, clinical trials on this issue involved very few drugs and defined flare differently across studies, rendering it difficult to make meaningful comparisons across studies. So, further studies should include other biological DMARDs and use a validated flare criterion. Long-term efficacy and safety should be evaluated to determine optimal dosages, while minimising the incidence of side-effects and cost, and satisfying the precondition of efficacy.

In conclusion, in consideration of the balance between efficacy and safety, our systematic review found no significant benefit of continuing biological DMARDs as compared with down-titrating biological DMARDs. Nonetheless, further trials are needed to elucidate the long-term efficacy and safety of DMARDs.

References

1. WELSING PM, VAN GESTEL AM, SWINKELS HL, KIEMENEY LA, VAN RIEL PL: The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis Rheum* 2001; 44: 2009-17.
2. MATCHAM F, SCOTT IC, RAYNER L *et al*.: The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2014; 44: 123-30.
3. CALLHOFF J, WEISS A, ZINK A, LISTING J: Impact of biologic therapy on functional status in patients with rheumatoid arthritis--a meta-analysis. *Rheumatology* (Oxford) 2013; 52: 2127-35.
4. PIERREISNARD A, ISSA N, BARNETCHE T, RICHEZ C, SCHAEVERBEKE T: Meta-analysis of clinical and radiological efficacy of biologics in rheumatoid arthritis patients naive or inadequately responsive to methotrexate. *Joint Bone Spine* 2013; 80: 386-92.
5. AZEVEDO AF, PETRIBU KC, LIMA MDE N *et al*.: Quality of life of patients with rheumatoid arthritis under biological therapy. *Rev Assoc Med Bras*. 2015; 61: 126-31.
6. 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.
7. BONGARTZ T, WARREN FC, MINES D, MATTESON EL, ABRAMS KR, SUTTON AJ: 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.
8. O'MAHONY R, RICHARDS A, DEIGHTON C, SCOTT D: Withdrawal of disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2010; 69: 1823-6.
9. VAN HERWAARDEN N, DEN BROEDER AA, JACOBS W *et al*.: Down-titration and discontinuation strategies of tumor necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. *Cochrane Database Syst Rev* 2014; 9: CD010455.
10. VAN VOLLENHOVEN RF, OSTERGAARD M, LEIRISALO-REPO M *et al*.: Full dose, reduced dose or discontinuation of etanercept in rheumatoid arthritis. *Ann Rheum Dis* 2016; 75: 52-8.
11. SMOLEN JS, NASH P, DUREZ P *et al*.: Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 2013; 381: 918-29.
12. SMOLEN JS, LANDEWÉ R, BREEDVELD FC *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509.
13. KOBELT G: Treating to target with etanercept in rheumatoid arthritis: cost-effectiveness of dose reductions when remission is achieved. *Value Health* 2014; 17: 537-44.
14. HIGGINS JPT, GREEN S: Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. In.; 2008.
15. VAN HERWAARDEN N, VAN DER MAAS A, MINTEN MJ *et al*.: Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. *BMJ* 2015; 350: h1389.
16. FAUTREL B, PHAM T, ALFAIATE T *et al*.: Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study). *Ann Rheum Dis* 2016; 75: 59-67.
17. HASCHKA J, ENGLBRECHT M, HUEBER AJ *et al*.: Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping antirheumatic therapy: interim results from the prospective randomised controlled RETRO study. *Ann Rheum Dis* 2016; 75: 45-51.
18. RAFFEINER B, BOTSIOS C, OMETTO F *et al*.: Effects of half dose etanercept (25 mg once a week) on clinical remission and radiographic progression in patients with rheumatoid arthritis in clinical remission achieved with standard dose. *Clin Exp Rheumatol* 2015; 33: 63-8.
19. WESTHOVENS R, ROBLES M, XIMENES AC *et al*.: Maintenance of remission following 2 years of standard treatment then dose reduction with abatacept in patients with early rheumatoid arthritis and poor prognosis. *Ann Rheum Dis* 2015; 74: 564-8.
20. OKANO T, INUI K, TADA M *et al*.: FRI0137 Medication interval of adalimumab for rheumatoid arthritis patients might be extended after the achievement of low disease activity-Kabuki study. *Ann Rheum Dis* 2015; 74 (Suppl. 2): 471-471.
21. FAUTREL B, DEN BROEDER AA: De-intensifying treatment in established rheumatoid arthritis (RA): Why, how, when and in whom can DMARDs be tapered? *Best Pract Res Clin Rheumatol* 2015; 29: 550-65.
22. VAN DER MAAS A, KIEVIT W, VAN DEN BEMT BJ *et al*.: Down-titration and discontinuation of infliximab in rheumatoid arthritis patients with stable low disease activity and stable treatment: an observational cohort study. *Ann Rheum Dis* 2012; 71: 1849-54.
23. VAN HERWAARDEN N, HERFKENS-HOL S, VAN DER MAAS A *et al*.: Dose reduction of tocilizumab in rheumatoid arthritis patients with low disease activity. *Clin Exp Rheumatol* 2014; 32: 390-4.
24. KUIJPER TM, LAMERS-KARNEBEEK FB, JACOBS JW, HAZES JM, LUIME JJ: Flare rate in patients with rheumatoid arthritis in low disease activity or remission when tapering or stopping synthetic or biologic DMARD:a systematic review. *J Rheumatol* 2015; 42: 2012-22.