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Reduction of biologics in rheumatoid arthritis treatment: a systematic review and meta-analysis

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Abstract
This systematic review assesses the effectiveness and safety of reducing the dose of biological drugs in patients with rheumatoid arthritis at low disease activity, compared to standard dose treatment. Clinical outcomes data were collected and summarized in meta-analysis of standardized mean difference or relative risk. Most outcomes were non-significant.

Key words:
Rheumatoid arthritis, biologics, dose reduction.

Introduction

Reduction of biologics after reaching low disease activity rheumatoid arthritis has been tested in clinical trials[1]. The aim of this systematic review is to assess the effectiveness and safety of the reduction of biologics drugs in patients with rheumatoid arthritis in low disease activity.

Results and Discussion

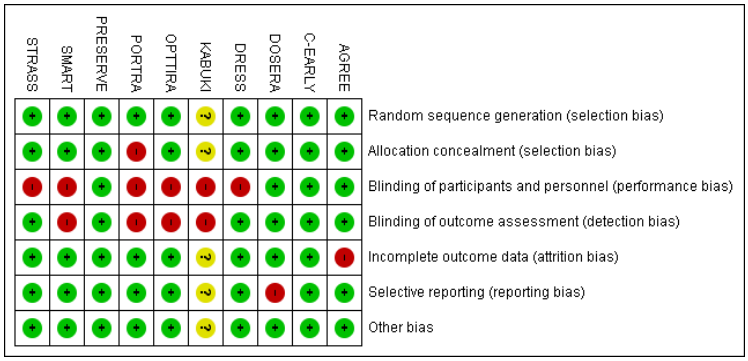
We searched MEDLINE, Embase, Scopus and The Cochrane Library for randomized controlled trials that reduced or spaced the dose of biologics in patients at low disease activity or remission state compared with maintenance. 1,420 patients were included, from 10 studies selected out of 1,325 retrieved publications. Risk of bias was high for more than half of studies in blinding of participants, personnel and outcome assessors (Figure).

Meta-analysis calculated on Stata showed that outcomes were not significantly different when comparing patients that reduced or maintained the usual dose of biologics (Table).

Table. Summary of findings

Outcome	Effect (95% CI)	Studies (N)
Dichotomous (relative risk)		
Low disease activity (LDA)	0.89 (0.77, 1.02)	10
Adverse events (AE)	1.02 (0.95, 1.10)	9
Serious AE	0.99 (0.70, 1.40)	8
Continuous (standardized mean difference)		
Health assessment questionnaire (HAQ)	0.12 (-0.05, 0.28)	5
Disease activity score (DAS-28)	0.1 (-0.03, 0.23)	6
Radiographic Progression	0.06 (-0.27, 0.14)	1
Patient global assessment (PGA)	0.14 (-0.03, 0.31)	2
Time to flare	-2.23 (-2.87,-1.6)	1

Figure 1. Risk of bias assessment



LDA had a significant heterogeneity (I^2=55%). In the subgroup meta-analysis, studies that were blinded had no heterogeneity, while it remained high in open label studies (I^2=69%).

LDA, HAQ and DAS28 were rated as very low quality of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[2], and the others outcomes were rated as low quality. More than half of the patients in the meta-analysis came from studies sponsored by the pharmaceutical industry, thus downgrading the evidence due to possible publication bias. Imprecision (all outcomes), inconsistency (LDA) and risk of bias (DAS28 and HAQ) also contributed for rating down the evidence.

Conclusions

Available evidence shows no differences in clinically relevant outcomes from reduction of biologics compared to regular doses. The limited number of studies and the low certainty of evidence reduce the confidence in the findings, which needs to be monitored to better inform patients and clinicians.

[1]1. Van Herwaarden, Noortje 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;29(9):CD010455.
2. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924-26.