Safety of combination therapy with two bDMARDs in patients with rheumatoid arthritis: a systematic review and meta-analysis

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Abstract

Objectives: We performed a systematic review and meta-analysis of the current literature to assess the safety of combining two biologic disease-modifying antirheumatic drugs (bDMARDs) in the treatment of rheumatoid arthritis (RA).

Methods: We systematically searched for controlled studies evaluating safety in patients with RA treated with two bDMARDs independently of dose-regimen. Databases used were MEDLINE (via Pubmed), EMBase, Cochrane Library, Scopus, ClinicalTrials.gov, and the WHO International Clinical Trials Registry platform. A meta-analysis was performed between groups on combination therapy and patients on single therapy using random effects model calculating odds ratio (OR) as well as 95% confidence interval (CI). The primary outcome was the rate of serious adverse events (SAEs).

Results: Six studies with a total of 623 patients (410 on combination therapy and 213 on single therapy) were included. Median follow-up was 9.5 months (range 6-12 months). There was a significant increase in SAEs in the combination group (14.9 vs 6.0%, OR 2.51, 95% CI 1.29-4.89, I^2 0%) as well as in total adverse events (94.6 vs 89.1%, OR 2.07, 95% CI 1.11-3.86, I^2 0%). When performing subgroup analysis in patients receiving only full-dose of both bDMARDs there was a significant increase in serious infections (6.7 vs 0.6%, OR 5.58, 95% CI 1.25-24.90, I^2 0%) and the risk of SAEs remained significantly higher (17.1 vs 6.2%, OR 2.72, 95% CI 1.30-5.69, I^2 0%).

Conclusion: Our findings suggest that combination therapy with two bDMARDs in RA appears to increase the risk of SAEs during the first twelve months of treatment.

Introduction

Since the advent of biologic disease-modifying antirheumatic drugs (bDMARDs) the management of patients with rheumatoid arthritis (RA) has improved dramatically. Several bDMARDs that target different key players of the immune-regulatory pathways, such as proinflammatory cytokines and T and B cells, are currently available for RA (1). To date, there are numerous efficacious bDMARDs including tumor necrosis alpha inhibitors (TNFi) (infliximab, etanercept, adalimumab, certolizumab, golimumab), an interleukin-1 (IL-1) receptor antagonist (anakinra), interleukin-6 (IL-6) pathway inhibitors (tocilizumab, sarilumab, sirukumab), a B-cell depleting agent (rituximab) and an inhibitor of T-cell costimulation (abatacept). Current therapeutic goals are aimed at achieving remission as assessed by different disease activity scores (2,3) since this will prevent progression of joint damage and deformity (4). However, about 20% to 40% of patients treated with biologic therapies fail to achieve remission due to acquired therapeutic resistance, secondary failure or intolerance, consequently requiring additional treatment (5–8).

Combining anticytokine agents has been evaluated in animal models of arthritis resulting in synergistic improvement in the symptoms when compared to treatment with either agents alone (9,10). Moreover, recent data evaluating biologics that simultaneously target two molecules (dual target-directed agents) suggest it to be a promising strategy for RA (11–14).

Patients with RA are prone to infection (15) and several studies confirmed the increased risk of infectious events among patients treated with biologic agents (16–18). Hence, the safety and tolerability of combining different biologic agents is one of the major concerns of this treatment approach. Thus, we performed a systematic review and meta-analysis of the current literature to assess the safety of combining two bDMARDs in the treatment of patients with RA.

Methods

Search strategy

We performed a systematic review of the literature with meta-analysis of studies in which any combination of two bDMARDs approved for therapy in RA was assessed in the following databases: MEDLINE (via PubMed), EMBase, the Cochrane Library, Scopus, ClinicalTrials.gov, and the WHO International Clinical Trials Registry platform. The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines (19). Keywords used were “rheumatoid arthritis”, “biological products” and “combination” (**figure 1**). No limits were applied. We screened reference lists of relevant articles to ensure that no relevant publications were overlooked. The research clinical question was formulated according to the PICOs (Population, Intervention, Comparison, Outcome and Study design) method (20) (**supplementary table 1**).

Study selection

Studies which met the following criteria were included: (1) randomized, double-blind, placebo-controlled clinical trials (RCTs); or (2) observational or non-randomized comparative studies that recorded safety events; and (3) patients aged 18 years or over with diagnosed RA as defined by the ACR 1987 and/or ACR/EULAR 2010 (21,22) and (4) studies in patients treated with at least two bDMARDs (including infliximab, etanercept, adalimumab, certolizumab, golimumab, anakinra, abatacept, rituximab, and tocilizumab) independently of dose-regimen. The titles and abstracts of articles identified were reviewed independently by two rheumatologists (GB, JHS) and discordant evaluations were reviewed until consensus was reached.

Data extraction and management

Two reviewers (GB, JHS) independently extracted data for each study, including characteristics of the studies, demographic and disease characteristics of patients included in each study, evaluation criteria for safety, results and author’s conclusions. Risk of bias assessment for RCTs was performed using the Cochrane risk of bias tool as described in the Cochrane Handbook (23). Risk of bias for observational studies was

examined using a pre-specified scale based on the Newcastle-Ottawa scale (24). A serious adverse event (SAE) was defined as an adverse event that met any of the following criteria: was fatal; was life threatening; resulted in or prolonged hospitalization; resulted in persistent or marked disability or incapacity; was cancer; resulted in an overdose; resulted in the development of drug dependence or drug misuse; or was an important medical event. Infections were considered serious if they met criteria for an SAE or required intravenous antibiotics (25).

Statistical analysis

Studies were included in the quantitative synthesis if numerical data were extractable. The primary outcome was the rate of serious adverse events independently of dose-regimen (full and tapered dosages). Secondary outcomes were the risk of overall adverse events, overall infections and serious infections independently of dose-regimen. Moreover, we performed subgroup analysis of the primary and secondary outcomes on the studies in which patients received exclusively full dosage of bDMARDs as well as in studies in which patients received tapered dosage of at least one bDMARD. Extracted data were presented as number and percentage for qualitative variables, and as mean and standard deviation (or median and minimum, maximum) for quantitative variables. Heterogeneity between studies was assessed using the Cochran Q statistic and I^2 test. A random effects model was used independently of the existence or absence of heterogeneity between the results of the studies because results of studies with different design and patients' characteristics were pooled. The Mantel–Haenszel method was used with a random effects model, to generate an Odds ratio (OR) and 95% confidence intervals (CIs) for all included studies. Sensitivity analyses were performed. All analyses were performed using R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

1. Literature search results and study characteristics

Initially, 719 potentially relevant studies were screened and 713 were excluded (**figure 1**). After manually searching reference lists, reports of 6 studies were included by

consensus for qualitative synthesis; they were all included for meta-analysis. Among these six studies, five were clinical trials (26–30) and one was a cohort study (31). Median follow-up was 9.5 months (range 6-12 months). Safety was the primary outcome in three studies (3/6) (27,29,31). bDMARDs used in combination therapy were: TNFi and anakinra in one study (26), TNFi and abatacept in two studies (27,28), TNFi and rituximab in two studies (29,31), abatacept and anakinra in one study (27) and rituximab and tocilizumab in one study (30).

Table 1 gives a brief overview of these studies. Risk of bias in all studies was moderate to good (**supplementary table 2 and 3**).

This systematic review involved 623 patients: 410 patients were treated with the combination of two bDMARDs (combination group) and 213 patients were treated with one bDMARD alone or one bDMARD plus placebo (control group).

2. Safety of combination therapy with two bDMARDs in RA patients independently of dose-regimen (full and tapered dosages)

2.1. Overall adverse events (AEs)

Five studies (26–30) compared overall AEs between combination and control groups and were included in meta-analysis (**figure 2A**). One study (31) was excluded due to unavailable data on overall AEs. Pooled results showed an increase in overall adverse events in patients receiving combination therapy with two bDMARDs as compared to control group (94.6 vs 89.1%, OR 2.07, 95% CI 1.11-3.86, I^2 0%).

2.2. Serious adverse events (SAEs)

Five studies (26–30) that recorded SAEs were included in the meta-analysis (**figure 2B**). One study was excluded due to unavailable data on SAEs (31). On pooled analysis there was an increase in SAEs in the combination group as compared to control group (14.9 vs 6.0%, OR 2.51, 95% CI 1.29-4.89, I^2 0%). Among the studies which recorded mortality (26–29) only one death was recorded in the combination group in the study of Genovese et al (26).

2.3. Overall incidence of infections

Five studies (26,27,29–31) that recorded incidence of infections between combination and control groups were included in the meta-analysis (**figure 2C**). One study (28) was

excluded due to unavailable data on overall infectious events. Although four of the studies were randomized trials and one was observational, we considered that there was enough similarity and the outcomes were hard enough not to be influenced by the design. Pooled analysis showed no increased risk of infections between the two groups (52.9 vs 46.6%, OR 1.18, 95% CI 0.81-1.74, I^2 0%).

2.4. *Serious infections*

Six studies (26–31) that recorded serious infections were meta-analyzed (**figure 2D**). We observed an increase not reaching statistic significance in serious infections in combination group as compared to control group (5.4 vs 0.47%, OR 3.46, 95% CI 1.00-11.97, I^2 0%).

2.5. *Total neoplasms*

Only two studies (27,31) recorded neoplastic events during follow-up and therefore meta-analysis was not feasible. In the study of Weinblatt et al (27) there was an increased rate of neoplasms in the combination group (abatacept plus TNFi or abatacept plus anakinra) as compared to control group (TNFi or anakinra plus placebo) (6.8 vs 1.6%). In the study of Blank et al (31) there were no cases of neoplasms in both groups (rituximab plus etanercept vs etanercept alone).

Sensitivity analysis on overall infectious events and serious infections independently of dose-regimen were performed after exclusion of the only non-randomized study (31) (see **supplementary figure 1**).

3. *Safety of combination therapy with two bDMARDs in RA patients receiving only full dosage of bDMARDs*

When performing subgroup meta-analysis on the studies in which patients received exclusively full dosage of bDMARDs (**figure 3**), the risk of SAEs in the combination group remained significantly higher (17.1 vs 6.2%, OR 2.72, 95% CI 1.30-5.69, I^2 0%) (26,27,29) (**figure 3A**). On the other hand, the risk of overall AEs was not statistically different between the two groups (94.4 vs 89.0%, OR 2.15, 95% CI 1.00-4.62, I^2 0%) (**figure 3B**). Regarding infectious events, the risk of serious infections remained significantly higher in the combination group when compared to control group (6.7 vs

0.6%, OR 5.58, 95% CI 1.25-24.90, I^2 0%). Conversely, the risk of overall infections was not different between the two groups (55.6 vs 46.0%, OR 1.28, 95% CI 0.85-1.94, I^2 0%).

Sensitivity analysis on overall infectious events and serious infections in patients receiving exclusively full dosage of bDMARDs were performed after exclusion of the only non-randomized study (31) (see **supplementary figure 2**).

4. Safety of combination therapy with two bDMARDs in RA patients receiving tapered dosage of at least one bDMARD

We performed subgroup meta-analysis on the studies in which patients received tapered doses of at least one of the bDMARDs in the combination group (**supplementary figure 3**). Results showed no statistical significance in the risk of overall AEs (94.6 vs 89.9%, OR 1.89, 95% CI 0.76-4.69, I^2 0%), SAEs (12.3 vs 3.4%, OR 2.36, 95% CI 0.68-8.14, I^2 8%) or serious infections (3.7 vs 0.0%, OR 2.54, 95% CI 0.42-15.26, I^2 0%). Due to insufficient data, meta-analysis of the risk of overall infectious events was not performed.

Discussion

To our knowledge, this is the first systematic review with meta-analysis evaluating the safety of the combination of two bDMARDs in patients with RA. Our findings confirm some previous individual studies results suggesting increased risks of SAEs in particular serious infections in RA patients receiving two bDMARDs concomitantly (26–28).

RA confers a substantially increased risk of morbidity and mortality related to cardiovascular, respiratory, and infectious diseases (32,33). A recent study reported that 8% of patients with RA require hospital admission each year due to serious infections (15). A previous network meta-analysis found that in the short term biologics were associated with statistically significant higher rates of total AEs and serious infections (34). Recently, data from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) including 19 282 patients confirmed higher rates of

serious infections with an incidence of 5.51 cases per 100 patients years (35). Hence, it was hypothesized that combining different bDMARDs could increase the risk of adverse events and serious infections.

Data regarding safety of combination therapy with different bDMARDs in RA are scarce. Our meta-analysis showed a modest but increased risk of total AEs, SAEs but not in overall infections and serious infections in patients treated with two bDMARDs concomitantly. Interestingly, the risk of serious infections was significantly higher in patients receiving only full dose of both bDMARDs thus suggesting that using higher doses may be associated with higher AEs in particular serious infections. Indeed, when we performed some exploratory analysis on the subgroup of patients who received tapered doses of at least one of the bDMARDs, we did not observe any significant increase in overall AEs, SAEs or serious infections. This should be interpreted with caution because of the low number of events with wide confidence intervals making these statistical results unstable. Nonetheless, the risk of the association of tapered doses of bDMARDs should deserve further investigation in order to clarify whether this could be a safe approach in selected RA patients. Of note, our literature search highlighted one study not fulfilling our selection criteria for meta-analysis showing that the safety profile of rituximab in combination with another bDMARD was similar with that reported for rituximab with other non biologic DMARD (36). However, this was an uncontrolled study.

The overall incidence of SAEs in the included studies in our systematic review was 14.9%. The incidence of SAEs reported in previous clinical trials of bDMARDs used either in monotherapy or in association with other csDMARDs (conventional synthetic DMARDs) seems to be slightly lower than that observed in our study: 11% (11/88) with infliximab (5), 12% (33/274) with etanercept (37), 6% (13/212) with tocilizumab (38), 10.5% (27/258) with abatacept (39), 10% (4/40) with rituximab (40) and 7.7% (86/1116) with anakinra (41).

Efficacy of combination therapy has also been evaluated in the included studies. Overall, data from the five clinical trials included (26–30) showed modest clinical effects with no clear evidence of an efficacy advantage in RA patients receiving combination therapy. Yet, when focusing on the only observational study included (31) combination therapy (rituximab and etanercept) seems to show clinical and biological benefits in patients with RA in a “real-life” setting. Since there are substantial differences in RA patients characteristics between randomized-controlled trials and

observational studies (42) the question of efficacy of a combination strategy should deserve further investigation in real-world settings.

Our systematic review with meta-analysis has several strengths. The studies we included showed high-quality scores. Furthermore, most of the studies were randomized clinical trials with only one observational controlled study (31). Indeed, when performing sensitivity analysis after exclusion of the observational study the risk of adverse events remained stable. However, limitations of this study should also be considered when interpreting the findings, in particular the small number of studies included, different combination therapy approaches used, unavailable data on average dose of corticosteroid and methotrexate at inclusion and short follow-up period up to 12 months.

This study is timely since dual-target directed agents targeting simultaneously different cytokines involved in the pathogenesis of RA are currently being developed (43,44). In fact, dual inhibition of TNF and interleukin-17A produced an acceptable safety profile in patients with RA when compared to TNF inhibition with adalimumab alone. However, safety data on dual-target agents in RA are scarce. Therefore any direct comparison between dual-target with bi-specific antibodies and combination therapy with two separate agents should be taken with caution.

Conclusion

In summary, our findings suggest that combination therapy with two bDMARDs appears to increase the risk of SAEs during the first six to twelve months of treatment especially in patients receiving full dose of both bDMARDs. Using tapered doses of bDMARDs seems to be a safer approach; further studies are warranted to confirm this signal. Therefore, clinicians should assess the risk/benefit ratio before considering a combination therapy in the management of patients with RA.

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Figure legends

Figure 1. Flowchart of the literature search.

Figure 2. Forest plot of mean differences between combination therapy and controls (‘monotherapy’) in overall adverse events (A), serious adverse events (B), overall infectious events (C), serious infections (D) independently of dose-regimen (full and tapered dosages).

Figure 3. Forest plot of mean differences between combination therapy and controls (‘monotherapy’) in overall adverse events (A), serious adverse events (B), overall infectious events (C), serious infections (D) in patients receiving only full dosage of biologic disease-modifying antirheumatic drugs.

Table legends

Table 1. Summary of studies included in meta-analysis

Figure 2

A

B

C

D

Figure 3

A

B

C

D