Safety of combination therapies in early rheumatoid arthritis: a systematic comparison between antirheumatic drugs and TNF inhibitors with methotrexate

We evaluated the frequency and type of adverse effects associated with combination disease-modifying antirheumatic drugs and TNF inhibitors combined with methotrexate (MTX) compared with MTX monotherapy by systematically reviewing trials in early rheumatoid arthritis. We identified 15 relevant trials by searching EMBASE, Medline and Cochrane databases (1960 to March 2010). Combination therapy gave more withdrawals for toxicity than MTX monotherapy. There was more nausea with combination disease-modifying antirheumatic drugs and more serious adverse events with TNF inhibitors combined with MTX. The total numbers of adverse events, serious infections, malignancies and deaths were similar with combination therapy and monotherapy. However, the short follow-up period may have been inadequate to detect new malignancies. Events in individual systems were uncommon and did not show major differences between groups. We conclude there is no evidence that intensive therapy in early rheumatoid arthritis causes unacceptable toxicity compared with MTX monotherapy.

KEYWORDS: biologics ■ combination therapies ■ disease-modifying antirheumatic drugs ■ drug toxicity ■ rheumatoid arthritis ■ systematic review

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Rheumatoid arthritis (RA) is a chronic inflammatory disease requiring long-term suppressive treatment. Early combination therapies using disease-modifying antirheumatic drugs (DMARDs) or TNF inhibitors with methotrexate (TNFi/MTX) have been shown to be more efficacious than DMARD monotherapy in terms of clinical outcomes, disability and radiological progression [1–3]. New guidelines all recommend the early use of these intensive therapies in the 'window of opportunity' [4,5,101]. As therapies become increasingly intensive and aggressive, drug toxicity is now a crucial issue.

Conventional synthetic DMARDs include MTX, sulfasalazine, hydroxychloroquine, leflunomide, cyclosporine and azathioprine. The majority of DMARD agents can cause bone marrow suppression, serious infections, liver damage and gastrointestinal disturbance. In addition, cyclosporine can also cause renal dysfunction, hirsutism and gingival hypertrophy. Toxicity of TNFi include serious infections, bone marrow suppression, reactivation of TB and serious infections. There are also concerns related to malignancy, worsening of heart failure and demyelination. Close monitoring of patients is recommended whilst on any synthetic DMARD or biological therapies. Evidence for risk of malignancy in TNF blockade is conflicting. A systematic review of infliximab and adalimumab found an increased risk of malignancy when compared with placebo therapy [6]. In addition, in the British Society for Rheumatology Biologics Register (BSRBR), patients with a history of malignancy were also at greater risk of developing new malignancies [7]. However, other registries (RABBIT and BIOBADASER) found no increase in malignancies in their cohorts compared with the general RA population [8,9].

In view of the adverse events related to individual DMARDs, there are concerns over the potential increase in toxicity when these agents are combined. This systematic review aims to compare the effects of combination DMARDs and anti-TNF with MTX (TNFi/MTX) to MTX monotherapy.

Methods

Search strategy

We searched EMBASE, Medline and Cochrane from 1960 to March 2010. The term early RA was combined with DMARDs, biological therapy or treatment. This was limited to English language and clinical trials. The titles and abstracts were then hand searched.

Selection criteria

The following criteria were used to select studies for further evaluation:

- The studies were randomized controlled trials (RCTs)
- The patients fulfilled the American College of Rheumatology classification criteria for RA

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- The disease duration was less than 3 years
- 'Treatment' arms comprised one or other or both of: combination DMARDs; and TNFi/MTX combination (infliximab, adalimumab or etanercept with MTX)
- 'Control' arm comprised of MTX monotherapy. We chose MTX monotherapy as this was the most commonly used DMARD monotherapy

Adverse events outcomes

The following adverse events outcomes were noted:

- Patient withdrawal due to toxicity
- Total adverse events
- Serious adverse events (total and by system)
- Nausea
- Malignancy
- Death

Quality of trials

The quality of the trials was judged by using the Jadad Scoring system [10].

Statistical analysis

Results were analyzed using Review Manager 5 (Cochrane Collaboration, Oxford, UK). The fixed effect odds ratio (OR) with Peto method was used to estimate the pooled effect sizes for all rare outcomes. Random effect OR was used for the outcome 'total adverse events' as this was not a rare event. For all meta-analyses, we performed Cochran's chi-squared test to assess between study heterogeneity and quantified I2 statistics. We considered a p-value of less than 0.05 as statistically significant.

Results

Studies identified

The preliminary search identified 459 citations: 426 citations were excluded based on search of titles and abstracts of these articles; 33 studies were selected for full text review; and 15 studies were excluded as they were follow-up studies of included trials. Two studies used pooled data from other trials and one study did not report any adverse event outcomes and therefore were excluded (Figure 1).

Table 1 shows the baseline characteristics of the patients. Seven RCTs compared combination DMARD therapies with MTX monotherapy, seven RCTs compared TNFi/MTX with MTX monotherapy and one trial included both treatment arms. The disease duration ranged from less than 6 to less than 36 months and the follow-up period was between 12 and 24 months. The average Jadad score was 3.93 (range: 2–5).

Withdrawals due to toxicity

All studies reported patient withdrawal due to toxicity. Both combination arms had more withdrawals due to toxicity when compared with MTX monotherapy. In total, 58 out of 511 (11%) patients were withdrawn due to toxicity in the combination DMARDs arm compared with 28 out of 505 (6%) patients in the MTX arm. The fixed effect OR was 2.28 (95% CI: 1.39–3.73). The patient withdrawals due to toxicity in patients treated with TNFi/MTX was 102 out of 1160 (9%) and for MTX monotherapy was 67 out of 1058 (6%). The fixed effect OR was 1.44 (95% CI: 1.05–1.98). There was no heterogeneity (Table 2).

Total adverse events

Four RCTs comparing combination DMARDs with MTX monotherapy and four RCTs comparing TNFi/MTX with MTX monotheray reported total adverse events. In total, there were 170 out of 255 (42%) adverse events in the combination DMARDs arm and 151 out of 260 (58%) adverse events in the MTX arm. The random effects OR was 2.76 (95% CI: 0.57–13.30), whereas the total adverse events were 627 out of 739 (85%) for TNFi/MTX and 609 out of 724 (84%) for MTX monotherapy. The random effects OR was 1.52 (95% CI: 0.84–2.75).

Serious adverse events

In total, three RCTs reported 40 out of 285 (14%) serious adverse events in patients treated with combination DMARDs compared with 29 out of 278 (10%) in patients treated with MTX monotherapy. The fixed effects OR was 1.43 (95% CI: 0.86–2.24). Four RCTs reported more adverse events in the TNFi/MTX arm (147 out of 854, 17%) when compared with MTX monotherapy (85 out of 758, 11%). The fixed effects OR was 1.66 (95% CI: 1.26–2.20) (Table 2). Table 3 shows the number of serious adverse events reported by systems. The numbers of events in each system were rare in all treatment arms. There were no differences between the numbers of deaths between either combination treatment arms when compared with MTX monotherapy.

Serious infections

Four RCTs comparing combination DMARDs with MTX monotherapy reported rates of serious infections. In total, there were five out of 365 (1%) cases of serious infections reported in the combination DMARDs arm and 11 out of 358 (3%) in the MTX monotherapy arm. The fixed effects OR was 0.46 (95% CI: 0.17–1.24). Five RCTs comparing TNFi/MTX with MTX monotheray reported rates of serious infections. There were 38 out of 1137 (3%) and 25 out of 1029 (2%) cases of serious infections in subjects treated with TNFi/MTX and MTX monotherapy, respectively. The fixed effects OR was 1.35 (95% CI: 0.82–2.24) (Table 2).

Malignancy

Five RCTs comparing combination DMARDs with MTX monotherapy reported malignancies. In total, there were four out of 393 (1%) cases and seven out of 388 (2%) cases reported in the combination DMARDs arm and MTX monotherapy arm, respectively. The fixed effects OR was 0.58 (95% CI: 0.18–1.89). Five RCTs comparing TNFi/MTX with MTX monotheray reported malignancies. There were ten out of 1122 (0.9%) and eight out of 1015 (0.8%) cases of malignancies in subjects treated with TNFi/MTX and MTX monotherapy, respectively. The fixed effects OR was 1.15 (95% CI: 0.46–2.93) (Table 2).

Nausea

Three RCTs comparing combination DMARDs with MTX monotherapy and four RCTs comparing TNFi/MTX with MTX monotheray reported symptoms of nausea. In total, nausea was reported in 66 out of 220 (30%) of patients in the combination DMARDs arm and 40 out of 221 (18%) in the MTX monotherapy arm. The fixed effects OR was 2.06 (95% CI: 1.30–3.27). Nausea was reported in 74 out of 341 (22%) patients treated with TNFi/MTX and 69 out of 349 (20%) treated with MTX monotherapy. The fixed effects OR was 0.89 (95% CI: 0.61–1.28) (Table 2).

Length of follow-up

We carried out sensitivity analysis by subdividing the studies according to length of follow-up. In the combination DMARD group, five studies had 12 months follow-up and three had 24 months follow-up. The majority of studies using TNFi/MTX combination had 12 months follow-up. Only one study had 24 months follow-up (data not shown). The sensitivity analysis of combination DMARD studies showed that patient withdrawals due to toxicity were significantly higher at 24 months (OR: 2.44; 95% CI: 1.28–4.66). There was no difference at 12 months (OR: 1.87; 95% CI: 0.88–3.94). There were more episodes of nausea in the first 12 months (OR: 3.48; 95% CI: 2.00–6.08) and no difference at 24 months. It is also interesting that the studies with 12 months follow-up [11,12] both used MTX and sulfasalazine in combination, suggesting that this regime causes more nausea than other regimes. It is important to note that the 95% CI intervals are wide and, therefore, it is difficult to extrapolate from these results.

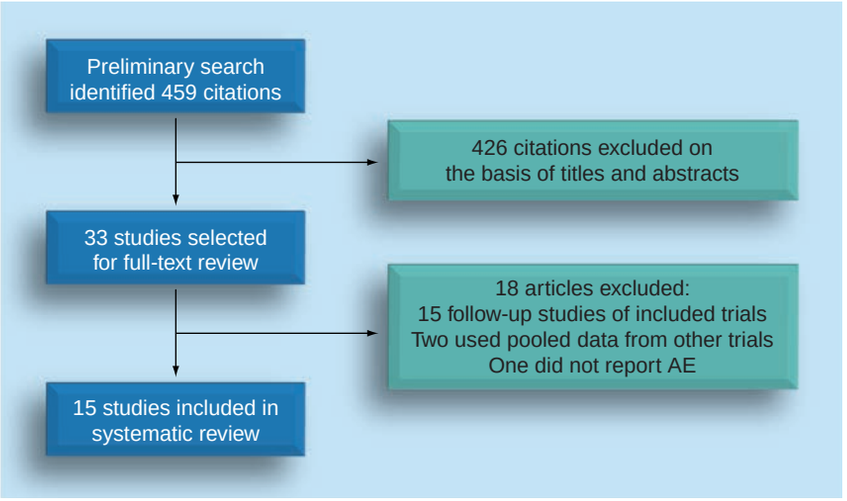

Figure 1. Selection of articles.
AE: Adverse event.

Discussion

Our systematic review of toxicity of combination therapies using TNFi/MTX or DMARDs showed some evidence of increased toxicity when compared with MTX monotherapy. In early RA RCTs, there were more patient withdrawals using combination DMARDs therapy or TNFi/MTX when compared with MTX monotherapy. More patients reported nausea when using combination DMARDs therapy and there were more serious adverse events using TNFi/MTX. However, the total numbers of adverse events, serious infections, malignancies and deaths did not differ significantly between the combination treatment arms and MTX monotherapy arms. The events reported per system were too rare to draw definitive conclusions.

Two previous systematic reviews have reported patient withdrawals due to toxicity [2,3]. Both supported the findings of our study. One reported that the numbers and types of

Table 1. Trial characteristics.

Study	Year	Disease duration (months)	Follow-up (months)	Jadad Score (1-5)	n	Combination arm therapies	MTX monotherapy arm					Combination arm					Ref.
							Mean age (years)	*Female (%)*	*RF+ve (%)*	*ESR*	*DAS*	*Mean age (years)*	*Female (%)*	*RF+ve (%)*	*ESR*	*DAS*	
Combination DMARDs																	
CARDERA	2008	<24	24	5	467	MTX†/CsA/Pred	54	67	66	–	5.8†	55	67	72	–	5.6†	[15]
Dougados *et al.*	1999	<12	12	4	209	MTX†/SSZ	50	74	62	46	4.1*	52	77	71	38	4.2*	[11]
BeST (step down)	2005	<12	12	3	508	Step down#	54	68	67	–	4.5**‡	55	65	65	–	4.3**‡	[14]
Haagsma *et al.*	1999	<12	12	4	105	MTX†/SSZ	55	66	94	20	4.7*	57	66	94	21	5.0*	[12]
CIMESTRA	2006	<6	12	5	163	MTX§/CsA/IA steroids	51	70	59	27	5.5†	53	64	70	28	5.3†	[16]
Ichikawa *et al.*	2005	<24	24	4	71	MTX‡‡/bucillamine	53	70	83	77	–	49	71	96	69	–	[17]
Marchesoni *et al.*	2003	<24	12	2	61	MTX††/CsA	49	90	74	65	5.1†	47	93	63	44	5.2†	[18]
O'Dell *et al.*	2006	<12	24	4	66	MTX‡/doxycyline	56	79	100	–	–	50	67	100	–	–	[19]
TNFi/MTX																	
Bejarano *et al.*	2008	<24	12	5	148	MTX§/ adalimumab	47	53	95	–	6.0†	47	58	96	–	5.9†	[20]
PREMIER	2006	<35	24	4	799	MTX§/ adalimumab	52	74	–	–	6.3†	52	72	–	–	6.3†	[21]
COMET	2008	<24	12	5	274	MTX§/etanercept	52	73	–	49	–	51	74	–	48	–	[22]
Quinn *et al.*	2005	<12	12	5	20	MTX¶/infliximab	53	–	60	–	–	51	–	70	–	–	[23]
BeST (TNFi/MTX)	2005	<12	12	3	508	MTX#/infliximab	54	68	67	–	4.5**‡	54	66	64	–	4.3**‡	[14]
Durez *et al.*	2007	<12	12	2	44	MTX§/infliximab	54	71	64	–	5.2***§	50	60	67	–	5.3***§	[24]
ASPIRE	2004	<36	12	4	1049	MTX†/infliximab	50	75	71	43	6.7†	50	68	73	44	6.7†	[25]
Taylor *et al.*	2004	<36	12	4	24	MTX¶/infliximab	51	–	–	36	5.1†	55	–	–	28	5.4†	[26]

**DAS28, **DAS44, ***DAS28CRP, †7.5–15 mg, ‡7.5–17.5 mg, §7.5–20 mg, ¶7.5–25 mg, #7.5–30 mg, ††10–20 mg,‡‡4–8 mg.*
CsA: Ciclosporin A; DAS: Disease Activity Score; DMARD: Disease-modifying antirheumatic drug; ESR: Erythrocyte sedimentation rate; IA: Intra-articular; MTX: Methotrexate; n: Number of patients randomized; Pred: Prednisolone; RF: Rheumatoid factor; SSZ: Sulfasalazine; TNFi/MTX: TNF inhibitors with MTX.

Table 2. Meta-analysis of toxicity outcomes.

Outcome	Treatment	Studies (n)	MTX monotherapy				Combination therapies				Fixed effects Peto OR (95% CI)	Heterogeneity	p-value	Ref.
			Cases	*Total*	*%*	*Range*	*Cases*	*Total*	*%*	*Range*				
Toxicity withdrawals	TNFi/MTX	8	67	1058	6.3	0–34	102	1160	8.8	0–35	1.44 (1.05–1.98)	10.77	NS	[11,12,15–19]
Nausea	Combo DMARDs	8	28	505	5.5	0–8	58	511	11.4	0–23	2.33 (1.43–3.77)	3.53	NS	[14,20–26]
	TNFi/MTX	2	69	349	19.8	16–53	74	341	21.7	24–50	0.89 (0.61–1.28)	2.13	NS	[20,22]
Serious adverse events	Combo DMARDs	3	40	221	18.1	35–117	66	220	30.0	10–33	2.06 (1.30–3.27)	11.62	0.003	[11,12,15]
	TNFi/MTX	4	85	758	11.2	8–34	147	854	17.2	13–51	1.66 (1.26–2.20)	24.74	<0.001	[14,20,22,25]
Serious infections	Combo DMARDs	3	29	278	10.4	0–21	40	285	14.0	0–23	1.43 (0.86–2.39)	1.34	NS	[12,14,15]
	TNFi/MTX	5	25	1029	2.4	0–8	38	1137	3.3	0–19	1.35 (0.82–2.24)	3.81	NS	[14,20–22,24,25]
Malignancy	Combo DMARDs	4	11	358	3.1	0–7	5	365	1.4	0–2	0.46 (0.17–1.24)	0.99	NS	[12,14–16]
	TNFi/MTX	5	8	1015	0.8	0–4	10	1122	0.9	0–4	1.15 (0.46–2.93)	2.53	NS	[14,20–22,25]
	Combo DMARDs	5	7	388	1.8	0–5	4	393	1.0	0–2	0.58 (0.18–1.89)	3.08	NS	[12,14–16,18]

Combo DMARDs: Combination disease-modifying antirheumatic drugs; MTX: Methotrexate; NS: Not significant; OR: Odds ratio; TNFi/MTX: TNF inhibitors with MTX.

Table 3. Total number of serious adverse events reported per system.

System	Treatment	MTX monotherapy					Combination therapies				
		Studies (n)	*Cases*	*Total*	*Range*	*%*	*Studies (n)*	*Cases*	*Total*	*Range*	*%*
Hepatobiliary	TNFi/MTX	2	1	341	0–1	0.3	2	3	349	0–3	0.9
	Combo DMARDs	2	7	104	0–5	6.7	3	3	67	1	4.5
Skin/hair	TNFi/MTX	0	0	0	0	0	2	2	349	0–1	0.6
	Combo DMARDs	1	1	69	1	1.4	2	3	39	1–2	7.7
Neurological	TNFi/MTX	1	1	268	1	0.4	1	4	274	4	1.5
	Combo DMARDs	1	0	30	0	0	1	1	28	1	3.6
Cytopenia	TNFi/MTX	0	0	0	0	0	0	0	0	0	0
	Combo DMARDs	1	1	15	1	6.7	2	2	184	1	1.1
Lung	TNFi/MTX	1	1	268	1	0.4	2	4	402	1–3	1
	Combo DMARDs	0	0	0	0	0	1	2	116	2	1.7
Gastrointestinal	TNFi/MTX	1	4	268	0–1	1.5	2	4	349	1–3	1.1
	Combo DMARDs	2	2	147	0–1	1.4	2	5	114	1–4	4.4
Death	TNFi/MTX	5	3†	1015	0–2	0.3	5	2†	1122	0–1	0.2
	Combo DMARDs	1	1	117	0–1	0.9	3	2	232	2	0.9

†In the COMET trial, there was one death. The drug allocation is still unmasked and we have therefore excluded this death.
Combo DMARDs: Combination disease-modifying antirheumatic drugs; MTX: Methotrexate; TNFi/MTX: TNF inhibitors with MTX.

short-term adverse events were also similar for biological and synthetic DMARDs [3], and the other found that there were increased patient withdrawals due to toxicity in the combination DMARDs groups but biological therapies were not included in their review [2]. By contrast, a recent meta-analysis of MTX monotherapy showed favorable long-term safety. There was no evidence of increased risk of mortality and infections. Assessment for differences in risk of cirrhosis and malignancy between groups was also inconclusive [13].

Based on all the available evidence of the superior efficacy of combination therapies, current national and international guidelines recommend the use of intensive therapies in early RA [4,5,101]. Our systematic review shows that in early RA, this intensive approach is justifiable. The American College of Rheumatology guidelines recommend the use of TNFi/MTX or combination DMARDs as first-line therapy, whereas the UK guidance is more restrictive with biological therapy as second-line agents. We found only one trial that compared these two regimes directly [14]. This trial did not show any difference in toxicity between the two treatment arms. Our systematic review carried out an indirect comparison of these two treatment regimes by using MTX monotherapy as the control treatment arm. We considered this to be the best approach for comparing TNFi/MTX combinations and combination DMARDs, as MTX is the most commonly used DMARD. We felt that this standardized the control arm of the indirect comparison. Both treatment arms had more patient withdrawals but only TNFi/MTX had more serious adverse events when compared with MTX monotherapy. This suggested that there is more toxicity associated with this regimen. We believe this supports the recommendation from the UK NICE guidance to start with combination DMARDs as first-line therapy.

There are several limitations of our study. There was considerable heterogeneity between the trials, in particular of studies comparing synthetic combination DMARDs and MTX monotherapy. Different combinations of agents were used in different dosages and different regimes. We specifically focused on RCTs that used MTX monotherapy as a control treatment. We considered that this provided the best approach for comparing combination DMARDs with TNF/MTX combinations as all these latter RCTs had MTX monotherapy arms. We recognized that although the BeST study used MTX as the initial monotherapy agent, it did use other agents in subsequent steps of therapy. However, as this was the only head-to-head study comparing combination DMARDs with TNFi/MTX, we felt that it was important to include it in our systematic review. Our study concentrated on reports from original trials with short follow-up periods (1–2 years). Adverse events such as malignancy may require much longer periods of follow-up to detect significant episodes. There were also differences

in the way adverse events were reported and therefore it was difficult to compare across the trials. Although patient withdrawals due to toxicity is a crude outcome, it is reported in all studies and therefore we felt that this was a useful outcome measure to capture. Lastly, although the majority of trials reported adverse events, they were not powered to address this. Therefore, additional toxicity information may be obtained from large registries with longer follow-up periods.

In conclusion, combination therapies using synthetic or biological agents increased patient withdrawals due to toxicity when compared with monotherapy. There were more serious adverse events using biologics with MTX, whereas nausea was an issue for combination DMARDs. There were no significant differences in total numbers of adverse events, serious infections, malignancies and deaths between the combination treatment arms and MTX monotherapy arms. Based on the available evidence, intensive therapies in early RA appear to be justified.

Future perspective

The treatment of RA continues to evolve. The number and diversity of biological treatments used continues to expand; they are given to increasing numbers of patients, and they are being used in combination with more DMARDs. In addition, there is growing interest in using combinations of biologics. All of these changes are likely to increase the risks of adverse events. As a consequence biologic registries and Phase IV clinical trials, which provide long-term surveillance data, will have increasing importance in ensuring risks of adverse effects do not increase.

Financial & competing interests disclosure

The authors are grateful for the support of the ARC and the NIHR. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- The use of combination therapies (synthetic disease-modifying antirheumatic drugs or TNF inhibitors with methotrexate [MTX]) is increasing.
- A total of 15 randomized controlled trials comparing combination therapies with MTX monotherapy were found to report adverse events and toxicity, but there is marked variability in the way these outcomes were reported.
- Combination therapies using synthetic drugs or biologics increased patient withdrawals when compared with monotherapy.
- There were more serious adverse events using biologics with MTX when compared with MTX monotherapy.
- More patients reported nausea when using combination disease-modifying antirheumatic drugs therapy.
- The total numbers of reported adverse events, serious infections, malignancies and deaths did not differ significantly between the combination treatment arms and MTX monotherapy arm.
- The events reported by systems were too rare to draw definitive conclusions.
- Based on the available evidence, intensive therapies in early rheumatoid arthritis appear to be justified.

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