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Tumor necrosis factor alpha inhibitors, methotrexate or both? An inquiry into the formal evidence for when they are to be used in rheumatoid arthritis

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ABSTRACT

Objective. *The relative high cost and potential side effects mandate careful scrutiny as to when tumor necrosis factor alpha (TNF) inhibitors should be used in everyday practice. We surveyed how TNF inhibitors performed in randomized controlled trials when compared to methotrexate in methotrexate naïve rheumatoid arthritis patients.*

Methods. *We identified all randomized controlled trials with TNF inhibitors and methotrexate. We surveyed A-whether the patients enrolled were methotrexate naïve or not; B-efficacy outcomes and C-radiographic outcomes.*

Results. *Four studies that had been reported to be conducted among methotrexate naïve patients were identified. TEMPO trial was not done entirely in methotrexate naïve patients, contrary to what has been reported by its authors. Among these studies the methotrexate naïve arms did as well as the TNF inhibitor alone. The combination was better than either drug alone. Among the 6 studies in which the methotrexate failure patients had been enrolled, the TNF inhibitors always performed better when analyzed head to head with the methotrexate alone arms.*

Conclusions. *Available data indicate that TNF inhibitors are superior to solo methotrexate use only in the setting of combination treatment.*

Introduction

Tumor necrosis factor alpha (TNF) inhibitors were introduced in late 1990s and have been considered revolutionary in treating rheumatoid arthritis (1). It is, on the other hand, to be noted the outcome in rheumatoid arthritis had already considerably been improved, as compared to the earlier times, when TNF inhibitors were first introduced (2). This has been taken as primarily due to the early and aggressive utilization of disease modifying anti-rheumatic drugs (DMARDs), especially methotrexate, then already in use. Remission has become a realistic goal utilizing this aggressive approach (3).

While TNF inhibitors have been useful additions to our arsenal, methotrexate remains the most commonly prescribed DMARD, the anchor in rheumatoid arthritis treatment (4). This, in addition to the relative high costs and potential side effects (5), mandates careful scrutiny as to when and where TNF inhibitors should be used in everyday practice. To this end we set out to examine the available evidence related to clinical outcomes of TNF inhibitor and methotrexate use in rheumatoid arthritis when they have been compared head to head in double blind randomized controlled trials where the TNF inhibitor was tested specifically among the methotrexate naïve patients.

Methods

We first identified all randomized controlled trials of etanercept, infliximab and adalimumab in rheumatoid arthritis where a comparator arm was solo methotrexate. We searched PubMed for etanercept, infliximab and adalimumab separately with limits of human, English and randomized controlled trial. All phase 1 trials, continuations of original trials, open label extensions and studies where the comparator was not methotrexate were excluded from the initial search.

This produced ten studies. We then selected out those studies that were conducted only among the methotrexate naïve patients. This further reduced the number to four. Among these four studies we tabulated in detail:

A) The results of the primary efficacy outcome measures;
B) The results of the primary radiographic outcome measure when available;
C) Any other efficacy and/or radiographic outcome measures reported.

Finally, the remaining 6 trials in methotrexate non-naïve patients where a TNF inhibitor was compared to a placebo arm were further tabulated specifically for the primary efficacy and radiographic outcome measures.

Results

Table I gives the pertinent demography, drugs used and the primary efficacy and radiological outcomes measured while Table II depicts the results of the efficacy and radiology outcomes.

Early Rheumatoid Arthritis (ERA)

Bathon *et al*. compared 10 and 25 mg twice a week injections of etanercept with weekly oral methotrexate in the ERA study (6). The primary efficacy outcome was ACR-N (7, 8) at 6 months and the primary radiographic outcome was the modified Sharp score changes (9, 10), as was used in all four studies, at 12 months.

As depicted in a graph in the original manuscript, the ACR-N, the primary clinical outcome, was significantly (p=0.05) in favor of the etanercept 25 mg x2/week arm at month 6. On the other hand, there was no significant change in radiological progression as judged by the Sharp score (1.00 *vs*. 1.59, p=0.11) at 12 months.

Apart from these changes in the stated primary outcomes, the following outcome changes have also been reported:

a. ACR20 (11) at 12 months, end of the study, was achieved by 72% of the patients in the etanercept 25 mg group and 65% of those in the methotrexate group (p=0.16).
b. There was a significant worsening in the radiographic score in the methotrexate group as compared to the etanercept groups at 6 months (1.06 *vs*. 0.57, p=0.001).

Infliximab in early rheumatoid arthritis (ASPIRE)

The infliximab trial (12) does not have an infliximab alone arm, due to the fact that FDA recommends that this medication be used in combination with methotrexate in the treatment of rheumatoid arthritis. The combination regimen had efficacy (38.9 *vs*. 26.4%, p<0.001) and radiographic outcomes that were better (Fig. 1) than when methotrexate was used alone.

PREMIER

In the PREMIER study (13), the solo methotrexate arm had a significantly higher ACR20 response compared to solo adalimumab use (63% *vs*. 54%, p=0.043). On the other hand, the mean radiographic scores were significantly in favor of patients using adalimumab (Fig. 1).

Table I. Demographic and study characteristics of 4 MTX naïve RCTs.

	ERA(6)	TEMPO(14)	IFX early RA(12)	PREMIER(13)
# patients	424	682	641	799
# TNF arm	207	223	NA	274
# MTX arm	217	228	282	257
# combination arm	NA	231	359	268
Double blind duration	12 m	12 m	12 m	12 m
Mean TJC at baseline	31	33	33	31
Mean SJC at baseline	24	23	22	21
Primary efficacy outcome	ACR-N 6m	ACR-N 6 m	ACR-N 12m	ACR50 12m
Primary radiographic outcome	Sharp@12m	Sharp@12m	Sharp@12m	Sharp@12m

#: number; TNF: tumor necrosis factor inhibitor; MTX: methotrexate; TJC: tender joint count; SJC: swollen joint count; RCTs: randomized controlled trials.

Table II. 12-month efficacy and radiographic outcomes in 4 MTX naïve RCTs .

Study (reference)	ACR20	ACR50	ACR 70	ACR N	Sharp	NNT
ERA ETA (6)	72	NR*	NR*	NR*	1.00	15
ERA MTX	65	NR*	NR*	NR*	1.59	
TEMPO combi (14)	85	69	43	18.3	-0.54	12
TEMPO ETA	75	48	24	14.7	0.52	
TEMPO MTX	76	43	19	12.2	2.8	
IFX combi (12)	62.4	45.6	32.5	38.9	0.4	13
IFX MTX	53.6	32.1	21.2	26.4	3.7	
PREMIER combi (13)	73	62	46	NR	1.3	10
PREMIER ADA	54	41	26	NR	3.0	
PREMIER MTX	63	46	28	NR	5.7	

NR: not reported; NR*: values not given, only depicted in graphic form; TNF: tumor necrosis factor inhibitor; MTX: methotrexate; ETA: etanercept; IFX: infliximab; ADA: adalimumab; combi: combination; NNT: number needed to treat.

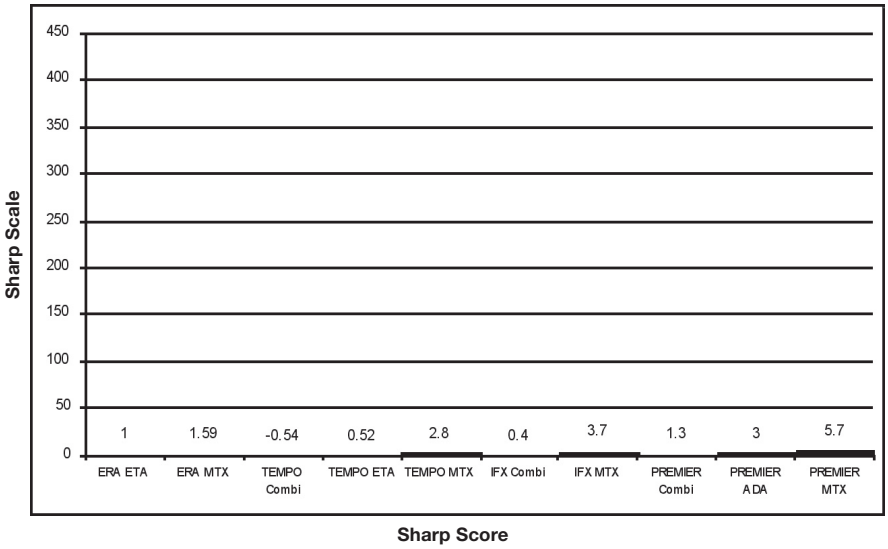

Fig. 1. Radiographic outcomes in randomized controlled trials with methotrexate naïve patients. TNF: tumor necrosis factor inhibitor; MTX: methotrexate; ETA: etanercept; IFX: infliximab; ADA: adalimumab.

TEMPO

This second study with etanercept (14) has been reported as being conducted among 3 groups of methotrexate naïve patients. On closer look one sees that over 40% of the patients in each arm (etanercept only, methotrexate only and etanercept + methotrexate combination)

had used methotrexate before the trial had began.

The primary clinical outcome at TEMPO was ACR-N at 6 months and the radiographic outcome was Sharp score at 12 months. In both parameters (see Table II for clinical outcomes and Figure 1 for radiology) the patients in etanercept and etanercept+methotrexate groups fared significantly better when compared to the patients in the solo metho-trexate arm.

We also calculated the numbers needed to treat (15) for the best reported outcome measure in these four trials. Table II also shows that these ranged from 10 -15.

Finally out of the ten randomized controlled trials with TNF inhibitors there were six studies where methotrexate failure patients were treated with a TNF inhibitor while the control arms received placebo in addition to methotrexate. In all of these studies TNF inhibitor arm did better than the placebo + methotrexate arms (Table III) (16-21).

Discussion

Of the four trials said to have been conducted among the methotrexate naive patients, the TEMPO trial had included, as noted above, considerable number of patients who had previously used methotrexate in all arms. A further important and negative issue with this trial has been an extension report (22) which we suggested was also fraught with methodological weaknesses (23) one of which was not explicitly stating that many of the originally enrolled patients had not been methotrexate naïve.

Considering that the infliximab early rheumatoid arthritis trial had no TNF inhibitor alone arm, hence did not provide head to head information with methotrexate, leaves the ERA and PREMIER studies where one can truly judge the efficacy of solo TNF inhibitor use over solo methotrexate use among those who used both of these agents for the first time. In these two trials, the changes in the primary efficacy outcome measure chosen by the investigators at the study inception turned out to be not significantly different among the TNF inhibitor and methotrexate alone arms. In fact, in the PREMIER study, methotrexate alone did better than adalimumab alone.

Table II shows that the mean tender and swollen joint counts were more than 30 and 20 respectively in these trials at entry, while we and others had previously reported that the majority of rheumatoid arthritis patients seen in everyday practice have less severe disease (24, 25).

In contrast to the at best modest clinical changes measured by any clinical outcome measure, the radiographic changes, as judged by the Sharp scores – modified Sharp score ranges 0-398 and combines joint space narrowing and erosion scores (9, 10) – fared numerically better in the arms using TNF inhibitors compared to methotrexate alone arms. However, these changes, although statistically significant, were rather modest changes on a scale that has the potential of more than a hundredfold change than what have been observed (Fig. 1). In addition, Sharp scoring takes 5 unit change as "clinically significant" and only in the PREMIER study methotrexate arm was the change in the Sharp score above 5.0 (5.7).

Table III. Efficacy and radiographic outcomes in MTX failure studies.

Study (reference)	ACR20 TNF+MTX	ACR20 MTX	Sharp TNF+MTX	Sharp MTX
ETA Weinblatt (17)	71	27	NR	NR
ETA Moreland (16)	59	11	NR	NR
IFX Maini (18)	50	20	NR	NR
IFX Lipsky (19)	42	17	1.3	7.0
ADA Weinblatt (20)	67	15	NR	NR
ADA Keystone (21)	59	30	0.1	2.7

TNF: tumor necrosis factor inhibitor; MTX: methotrexate; ETA: etanercept; IFX: infliximab; ADA: adalimumab; NR: not reported.

This "clinically not significant" radiographic score difference is frequently considered as a significant difference between methotrexate and TNF inhibitors. We disagree. In addition to being a very small difference among treatment arms, most of the difference is due to outliers, as most patients in these studies do not have a significant change in their radiographic scores as witnessed in the TEMPO trial, where the median change in Sharp score is zero in both etanercept and methotrexate arms.

Number needed to treat is another tool to report efficacy (15). The average number needed to treat from the four studies is around 12 patients. This would mean that for the estimated 2.5 million rheumatoid arthritis patients in the United States (26), if all were treated with either methotrexate or a TNF inhibitor, around 2.3 million would have fared the same with either therapy. With a yearly saving of over $10,000 per patient when methotrexate is used in place of a TNF inhibitor, this would amount to 23 billion dollars in savings each year. A further issue that needs to be addressed when making these crude cost estimates is that the related efficacy data in these trials have been collected only in the setting of severe disease to the degree seen in less than 15% of all rheumatoid arthritis patients (24, 25). This might conceivably also lessen the estimated number of rheumatoid arthritis patients who truly need the TNF inhibitors.

Among the three trials conducted among the truly methotrexate naïve patients (TEMPO excluded for including patients who had previously used methotrexate) it is clear that the TNF inhibitor plus methotrexate is superior to methotrexate use alone. Whether this warrants the initial use of combination therapy among those 0.2 million patients with rheumatoid arthritis alluded to in our crude medico-economic consideration above needs to be further considered. A formal reassessment of the adverse effect issues with such combination should also be included in this reappraisal.

Available data indicate that TNF inhibitors are superior to solo methotrexate use only in the setting of combination

treatment. Until further controlled data are available we suggest that the initial treatment of rheumatoid arthritis should not include TNF inhibitors unless the patient has high disease activity, for example tender and swollen joint count greater than 20, and propose that TNF inhibitors be reserved for combination treatment for patients who have inadequate or no response to initial methotrexate use.

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