
Efficacy of methotrexate in comparison to biologics in rheumatoid arthritis

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ABSTRACT

This paper reviews trials comparing the efficacy of MTX and biologic agents. So far, the clinical evaluations of 9 biologics have been published. Three TNF inhibitors – etanercept, adalimumab, golimumab – and the IL 6 receptor inhibitor tocilizumab have been investigated in MTX naïve patients using a parallel design. The trials had 3 treatment arms: monotherapies of MTX and of the biologic compound, and the combination of both. The other biologics – infliximab, certolizumab pegol, anakinra, rituximab, and abatacept – were investigated in patients who experienced inadequate response to MTX, and were treated with MTX + biologic agent versus MTX + placebo. That design does not provide a real comparison between MTX and the biologics but may indirectly give an indication of the relative efficacy of the different biologic agents.

In all trials providing a head to head comparison, MTX and biologics were similarly effective as measured by ACR and EULAR response criteria including clinical remission. In general, improvement started earlier with biologic treatment than with MTX therapy. Inhibition of radiological progression was stronger with biologics probably since TNF inhibitors, in addition to their anti-inflammatory effect, directly reduce osteoclast activity. The efficacy of biologics was significantly potentiated when they were combined with MTX.

Based on the trial results the efficacy of MTX may be underestimated: the initial dose of MTX was too low and was increased only gradually. The trial design with ITT analysis and LOCF may have been disadvantageous for MTX since more patients treated with MTX withdrew and thereby had less time under treatment. Folic acid supplementation may have reduced the efficacy of MTX by interfering with its

mechanism of action. Nonetheless, all trials confirmed a surprisingly good performance of MTX in comparison with biologics.

Introduction

This paper reviews trials comparing the efficacy of MTX with that of biologics in the treatment of rheumatoid arthritis. So far, nine biologics have been clinically evaluated in RA and are included in this overview. These are five TNF- α inhibitors, one IL 1 receptor antagonist, one IL 6 receptor inhibitor, one CD20+ B-cell inhibitor and one costimulation inhibitor.

MTX as the most widely used conventional DMARD was used as a competitor when evaluating the new compounds. Two types of designs have been used: a parallel design with head to head comparisons between the biologic agent and MTX; and a “step-up” design in patients who had experienced incomplete responses to methotrexate. Clinical trials with a parallel design have been published for three TNF- α blockers and the IL 6 receptor inhibitor. Most studies included three arms: MTX monotherapy, biologic monotherapy, and the combination of both agents. In most trials the initial MTX-dose was low, 10 or even only 7.5mg/wk, but could be increased to 20mg /wk within eight weeks, if needed. Folic acid therapy was given concurrently. Prednisone up to 10 mg/day was allowed. The patients had active disease and – in case of a direct head to head comparison of the monotherapies – were required to not have been treated with MTX or biologics before.

Clinical trials with a step-up design involved patients who experienced inadequate response to MTX, and were treated with MTX + biologic agent versus MTX + placebo. In these cases, the biologic agent was given in combination with MTX from the beginning of

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the evaluation process since that combination had been found to potentiate the efficacy of biologics significantly. Although these trials do not provide a real comparison of MTX with biologics they are also discussed briefly.

All studies described here were randomised double-blind controlled multicentre trials. As outcome criteria, ACR and EULAR response criteria were used. Radiological progression was measured in the joints of hands, wrists, and feet by means of the Sharp score, including the modifications by Van der Heijde and Genant. Statistical evaluation was performed using ITT analysis with Last Observation Carried Forward (LOCF).

Etanercept

ERA Trial

The ERA trial (1) was the first study in which etanercept and methotrexate (MTX) were compared directly. Six hundred and thirty-two patients with active early RA (mean disease duration ~12mo, CRP 4.0mg/dl, 24 swollen joints), who had not yet been treated with MTX, were randomised to be treated with either 25 or 10mg etanercept twice weekly or 7.5mg MTX weekly, which was increased to 15mg after 4 weeks and to 20mg after 8 weeks. The 10mg etanercept dose was significantly less effective than the 25mg dose, therefore, only the latter will be discussed further.

Treatment effect became apparent earlier with etanercept than with MTX. At most evaluation time points during the first six months, significantly more patients treated with etanercept 25mg had an ACR 20/50/70 response than those treated with MTX. After six months, no significant difference was seen between both groups. At 12 months, 65% of patients in the MTX group and 72% of patients in the etanercept group had an ACR 20 response ($p=0.16$). The excellent performance of MTX compared with a TNF-blocker initially was regarded as surprising by most experts. Etanercept had a more immediate effect than MTX also on radiographic progression, which may be explained in part by the low MTX doses applied for the first 4–8 weeks: at 6 months, the

total Sharp score had increased by 1.06 with MTX treatment and by 0.57 with etanercept treatment ($p<0.001$). During the second six months the progression was quite similar in both groups, and at 12 months the Sharp total score had reached 1.59 with MTX treatment and 1.00 with etanercept ($p=0.11$). Decreases in disease activity measures were correlated with the absence of radiographic progression.

Five hundred and twelve patients continued to receive the same treatment in an open-label extension (2): 74% of patients in the etanercept-group *versus* 59% in the MTX group completed two years of treatment. Both etanercept and MTX continued to be effective, and the ACR response rates remained similar to those seen at the end of the first year.

At two years, radiographs taken at all time points were scored again in a blinded fashion. In contrast to the first reading, this time significantly lower radiographic progression in the etanercept group was seen than in the MTX group during the first year of treatment. After 24 months, the mean total Sharp score had increased by 3.2 units in the MTX group, compared to 1.3 in the etanercept group ($p=0.001$). This corresponds to a yearly progression of only 0.3% *versus* 0.15% of the maximum Sharp score (448 units). It would take >150 years *versus* >300 years to reach a total Sharp score of 50% indicating a severe joint destruction. Fifty-one percent of patients treated with MTX *versus* 63% treated with etanercept had no increase in the Sharp score. This result was achieved even though only patients with a high potential of progression had been selected for this study (88% RF-positive, 88% erosive), and may be explained as an effect of early aggressive treatment.

TEMPO Trial

After TNF inhibition had turned out to be significantly more effective in combination with MTX in one study (3), several studies were designed as 3-arm trials including MTX, TNF-blockers, and the combination of both. One of these studies, the TEMPO trial (4), involved 686 patients with active RA (mean disease duration ~6.7 years,

mean CRP ~2.9mg/dl, DAS28 ~5.6) who were treated with MTX (escalated from 7.5 to 20mg/wk), with etanercept, or with the combination of both, over 3 years; 42% of patients had been treated with MTX previously, but previous MTX treatment had no significant influence on the outcome of the study in these patients.

At 24 weeks, the ACR-N area under the curve (AUC) was 12.2%-years for MTX and 14.7%-years for etanercept ($p=0.0034$), compared to 18.3%-years for the combination ($p<0.0001$). After one year, no significant differences were seen in all efficacy measures, including DAS improvement criteria and remission rates, between both monotherapies (ACR20 75% *vs.* 76%, ACR50 43% *vs.* 48%, DAS remission 13% *vs.* 16%, for MTX *vs.* etanercept). However, the combination group had significantly greater efficacy than each of the monotherapies.

The results of the radiological evaluation indicated that, although the clinical responses were comparable between the monotherapy groups, the increase of the total Sharp score at one year was significantly greater with MTX (2.8 Sharp units) than with etanercept (0.52 units). This can be explained by the fact that TNF blockers, in addition to their antiinflammatory effect, appear to inhibit radiological progression by a direct inhibition of osteoclast activity. Even more surprising was that the total Sharp change score including the 95% confidence interval became negative in the combination group (-0.54 (CI -1.00; -0.07)), clearly indicating not only inhibition of progression but also repair of erosions.

During the second year of the study (5), the ACR response rates as measured by ITT analysis remained unchanged, indicating sustained efficacy.

Only 332 patients (of 686 at baseline) completed three years of the trial (6). Significantly more patients from the MTX group (58%) than from the etanercept group (52%) or from the combination group (38%) had been withdrawn over the three years, only a minority for lack of efficacy. ACR response rates as well as DAS improvement and remission results over three

years were not significantly different between both monotherapies but were significantly greater in the combination group (Table I).

Within the MTX group, the proportion of patients in clinical remission at 3 years was nearly doubled using the completer analysis *versus* the ITT analysis with LOCF, while in the etanercept and combination groups the difference between both analyses was only 30% and 20%, respectively (Table II): more patients were withdrawn with MTX and therefore had less time to improve with treatment.

The mean radiographic progression over three years as measured with the Sharp total score was 5.95 in the MTX group, 1.61 in the etanercept group, and -0.14 (95% CI -1.07, 0.78) in the combination group. Again, the difference between combination and monotherapies was significant ($p < 0.05$). After three years, significantly fewer patients had radiographic remission (change score ≤ 0.5) in the MTX group (51%) than did patients in the etanercept group (61%) and the combination group (76%). According to the probability plot the proportion of patients with radiological progression appears to be 20% with MTX, 15% with etanercept and 5% with combination treatment.

COMET study

The COMET study (7) compared methotrexate monotherapy with the combination of MTX + etanercept in MTX-naïve patients with active RA and short disease duration (mean 9 months). The study did not include an etanercept monotherapy arm.

MTX monotherapy was less effective than combination treatment but still achieved a remarkable result: After 52 weeks, 28% of evaluable patients treated with MTX achieved a DAS28 remission compared with 50% of patients treated with the combination ($p < 0.0001$). Radiographic non-progression was seen in 59% of patients with MTX treatment *versus* 80% with combination therapy ($p < 0.0001$).

After one year, patients treated with the combination continued that treatment or switched to MTX. The original MTX group switched to the com-

Table I. Tempo trial: ACR responses (% of patients) over three years.

ACR response	MTX			Etanercept			Combination		
	20 %	50 %	70 %	20 %	50 %	70 %	20%	50%	70%
Year 1	75	43	19	76	48	24	85	69	43
Year 2	71	42	21	75	54	27	86	71	49
Year 3	70	44	21	71	46	26	85	61	42

Table II. Tempo trial: DAS 28 Remissions (% of patients) over 3 years.

DAS28 <2.6	ITT (LOCF) analysis			Completer analysis		
	MTX	Etanerc.	Etan. + MTX	MTX	Etan.	Etan. + MTX
Year 1	17.1	17.5	38.1* [#]	21.8	22.0	43.2* [#]
Year 2	18.9	22.4	42.4* [#]	25.6	29.6	53.7* [#]
Year 3	18.9	20.6	40.3* [#]	36.0	30.8	51.5 [#]

* $p < 0.01$ vs. MTX.

[#] $p < 0.01$ vs. etanercept.

bination or continued MTX treatment. As a result, patients treated with the combination during the second year performed better than patients treated with MTX irrespective if they had been treated with MTX or the combination in the first year.

One could conclude that it does not matter much if the initiation of combination treatment with a biologic agent is postponed for one year, and that the advantage of biologic treatment may be lost within one year.

Adalimumab

Adalimumab is a fully human anti-TNF monoclonal antibody.

The only large multicentre study including a head to head comparison of MTX with adalimumab was the PREMIER study (8). In that two-year, double-blind study, monotherapies with MTX and adalimumab were compared with each other and the combination of both agents in 799 MTX naïve RA patients with active early disease (mean time from diagnosis 0.6–0.7 years, CRP ~4.0mg/dl, DAS 28 ~6.3). Patients had a high potential of progressive disease: RF and/or erosions had to be present. The MTX dose started with 7.5mg and, if needed, could be increased to 15mg/wk up to week 8 and to 20 mg/wk in week 9. The adalimumab dose was 40mg every other week and could be increased to weekly application if the patients did not achieve ACR 20 response at week 16. The dose

was increased in 11% of the combination and 25% of the adalimumab monotherapy group, which had only weak influence on efficacy.

Significantly fewer patients treated with either MTX (65.8%) or adalimumab (60.9%) than patients in the combination group (75.7%) completed 2 years of the study ($p < 0.001$). Withdrawals for lack of efficacy were only a small proportion of all withdrawals: 18 /19/ 5% for the MTX, the adalimumab and the combination group.

The ACR response rates at 1 year of treatment were not different between both monotherapies but were significantly greater for the combination group ($p < 0.001$). For example, the ACR 50 response rate was 46% with MTX, 41% with adalimumab, *versus* 62% with combination treatment.

At 2 years of treatment, the ACR response rates were sustained, again with no difference between the monotherapies and superior efficacy of the combination therapy. Clinical remission (DAS 28 <2.6) was achieved in 25% each in both monotherapy arms, compared with 49% of patients treated with the combination ($p < 0.001$).

Radiographic progression as measured with the Sharp Total Score was significantly greater at 6 months, 1 year, and 2 years in patients in either monotherapy arm compared with those who had received combination treatment. After 2 years, the mean change was 10.4, 5.5 and 1.9 Sharp units for the MTX,

the adalimumab, and the combination group. ACR response rates were comparable in the two monotherapy arms. However, there was more radiographic progression in the MTX *versus* the adalimumab therapy arm at all time points measured ($p < 0.001$). No radiographic progression after 2 years was seen in 34% of patients in the MTX group, 45% in the adalimumab group and 61% in the combination group. Thus, inhibition of radiological progression was stronger with adalimumab than with MTX although there were small insignificant advantages for MTX in improving clinical and laboratory disease activity measures compared with adalimumab. Again, the combination was more effective than the monotherapies.

Golimumab

Golimumab is a human TNF alpha inhibitor binding with high affinity and specificity to soluble and transmembrane TNF alpha.

Golimumab as monotherapy and in combination with MTX was compared with MTX monotherapy in a 24 week study (9): 637 MTX-naïve patients with active RA (disease duration ~3.5 years, CRP ~2.5mg/dl, DAS 28~6.3) were randomly assigned to four treatment groups: MTX, golimumab 100 mg, golimumab 50mg + MTX, and golimumab 100mg + MTX. Oral MTX was escalated from 10 mg/wk to 20mg /wk by week 8. An ITT analysis did not show significant differences in efficacy between the groups: The proportion of patients achieving an ACR 50 response at 24 weeks (the primary endpoint of the study) were similar in the patients treated with MTX (29.4%) and those treated with golimumab (33.1%). No statistically significant difference was seen also for ACR50 responses between the MTX group (29.4%) and both combination treatment groups combined (38.4%; $p = 0.053$). Results of a post hoc ITT analysis excluding three randomised but untreated patients were significant, however (29.4% *vs.* 38.5%; $p = 0.049$). EULAR moderate or good responses were similar in the MTX and golimumab monotherapy groups (60% and 66%), while the combination treat-

ments were significantly more effective (~75% EULAR response). DAS28 remission using CRP levels occurred in 28% and 25% with both monotherapies and in ~38% with both combination treatments. The proportions of patients achieving EULAR-DAS28 response were lower when the ESR was used to define response criteria.

Infliximab

Infliximab, the first biologic introduced in the treatment of RA, is a chimeric monoclonal antibody to TNF- α . After recognition that MTX increased the therapeutic effect of infliximab and made it less immunogenic (3), all subsequent studies with infliximab were performed in combination with MTX. Therefore, a head to head comparison of infliximab alone and MTX alone does not exist.

In the ATTRACT trial (10), patients with active disease despite ongoing but insufficient therapy with MTX were treated with infliximab or placebo infusions every 8 or 4 weeks on background MTX. Within the 4 different combination groups, ACR20 response rates of about 60% were achieved, compared with ~25% in the MTX + placebo group. Respective ACR50 response rates were about 40% *vs.* 9%.

Radiographic progression was significantly greater in the MTX group than in the combination group (7.0 *vs.* 0.6 Sharp units). For the first time in a clinical trial (published in 1999), a large proportion of patients (39% up to 55%) in the combination groups had a decrease in their radiographic score (negative change score) indicating improvement. It was surprising that negative change scores could also be observed in 14% of patients within the MTX group. It must be emphasised that all patients in that study were inadequate responders to MTX. Most surprisingly, negative change scores occurred also in patients not responding clinically to infliximab treatment.

Certolizumab Pegol

Certolizumab pegol (CZP) is a novel PEGylated TNF alpha inhibitor with increased half life due to PEGylation. CZP monotherapy has not been com-

pared with MTX monotherapy. It has only been investigated as add-on therapy to MTX in comparison with placebo in patients who had an inadequate response to MTX treatment.

In the RAPID I trial (11), 982 patients with active disease (median DAS28 7.0, CRP 1.6mg/dl, ESR 44mm/h) were randomised to receive 200mg or 400mg CZP every two weeks or placebo in addition to their stable MTX dose. At week 24, the combination groups achieved an ACR20 response of ~60% compared with 13.6% for the placebo group ($p < 0.001$). A statistically significant difference was sustained to week 52. At one year, the radiological progression was 2.8 Sharp units in the placebo group compared with 0.2 and 0.4 units, respectively, for the combination groups.

As with infliximab, the true efficacy of MTX in relation to CZP cannot be estimated since all patients included in the study had failed to respond sufficiently to MTX. Moreover, the ITT analysis with LOCF is misleading since >60% of patients of the placebo group had already withdrawn at week 16 compared with only 21 and 17% of patients receiving the two CZP doses

Anakinra

IL1 activates target cells by binding to the IL1 receptor. Anakinra is an IL1 receptor antagonist binding to the receptor thereby blocking IL1.

Anakinra as monotherapy has not been compared with MTX monotherapy in the treatment of RA. However, one study compared anakinra with placebo, both on background MTX (12): 506 patients with active RA (disease duration ~10.5 years, ~20 swollen joints, CRP 2.7mg/dl, ESR 42mm) despite ongoing treatment with MTX (16 mg/week) were randomised to be treated with 100mg anakinra/day or placebo while continuing their MTX. After 24 weeks, significantly greater proportions of patients treated with anakinra compared with placebo achieved ACR20 (38% *vs.* 22%), ACR50 (17% *vs.* 8%), and ACR70 (6% *vs.* 2%) responses.

Tocilizumab

Tocilizumab is a humanised anti-IL6

receptor antibody that inhibits signaling of IL6 and thereby reduces its multiple proinflammatory activities.

Tocilizumab was compared head to head with MTX monotherapy within a 24 week study, the AMBITION trial (13): 673 patients with active RA (disease duration 6.4 years, CRP ~3.0mg/dl, ESR ~ 50mm/h, DAS28 6.8) were randomly assigned to 8mg Tocilizumab every 4 weeks or 7.5mg MTX/wk escalating to 20mg/wk within 8 weeks. One third of patients had been treated with MTX previously but not within the last six months.

About 93% of patients in both groups completed the 24 weeks of the study. The ACR response rates were significantly smaller with MTX than with tocilizumab treatment. At 24 weeks, the ACR20 response rate of MTX *versus* tocilizumab was 52.5% *vs.* 69.9%, the ACR50 response rate was 33% *vs.* 45%, respectively. A DAS28 remission was achieved in 12.1% and 37.6%, respectively. All these differences were statistically significant. Notably, mean CRP levels were within the normal range as early as week 2 with tocilizumab treatment, with persistently normal levels from weeks 12 to 24 in more than 90% of patients. Furthermore, mean hemoglobin levels increased remarkably with tocilizumab treatment.

The outcome of this study compares favorably with other trials (ERA, TEMPO, PREMIER) comparing TNF antagonists with MTX using a similar dose titration.

Rituximab

Rituximab is a chimeric monoclonal antibody that binds to CD20 and depletes the CD20 + population of B cells thereby blocking their role in the immuno- pathogenesis of RA.

A direct comparison of rituximab with MTX in MTX naïve patients has not been performed. However, there is a study comparing patients who continued their MTX although it was ineffective with patients who discontinued their ineffective MTX and were treated with rituximab as monotherapy.

That study (14) involved 161 patients with active RA (CRP 3.2mg/dl, ESR ~52mm/h, DAS28 6.9) despite

treatment with >10mg/wk MTX for at least 16 weeks. The patients were randomised to four treatment groups: Continuation of oral MTX at >10mg/week, rituximab without MTX, rituximab with cyclophosphamide, rituximab with continued MTX. The rituximab monotherapy was significantly more effective than the continuation of (ineffective) MTX treatment. At week 24, the ACR20 response rate in the MTX *versus* rituximab groups was 38% *vs.* 65%, the ACR50 response rate was 13% *vs.* 30%, and an ACR70 response was achieved by 5% *vs.* 15% of patients. The combination of rituximab with MTX was more effective than both monotherapies and as the combination of rituximab with cyclophosphamide.

Another study, the REFLEX trial (15), compared placebo with rituximab, both added to a current inadequate MTX treatment. Five hundred and twenty patients with active RA (disease duration ~12 years, CRP 3.8 mg/dl, ESR ~48 mm/h, DAS28 6.8) despite ongoing treatment with MTX were randomised to be treated with rituximab infusions or placebo infusions, both on background MTX. All patients had previously experienced an inadequate response to TNF-inhibitors.

Fifty-four percent of patients randomised to placebo and 82% randomised to rituximab completed the 24 weeks of the study. The ACR20 response rate in the placebo arm *versus* the rituximab arm was 18% *vs.* 51%, the ACR50 response was 5% *vs.* 27% of patients and the ACR70 response was 1% *vs.* 11%. The proportion of patients achieving a EULAR good or moderate response was 22% *vs.* 65%. There was only a trend towards less radiographic progression in the rituximab arm.

Abatacept

CTLA 4, a selective co-stimulation inhibitor, down-regulates CD28-mediated T-cell activation. Abatacept consists of human CTLA4 linked to human IgG1. It demonstrated efficacy in combination with MTX in clinical trials. However, a direct comparison of abatacept and MTX does not exist.

The AIM study (16) compared abatacept infusions with placebo infusions

in patients with active disease despite current treatment with MTX. Placebo was significantly less effective than abatacept already after 6 months. At 12 months, an ACR20 was achieved in 39.7% *vs.* 67.9%, an ACR50 in 16.8% *vs.* 39.9%, and an ACR70 in 6.5% *vs.* 19.8%, respectively, for the placebo *versus* the abatacept group. A low disease activity state (DAS28 ≤3.2) was reached in 9.9% *vs.* 42.5%, clinical remission (DAS28 ≤2.6) occurred in 1.9% *vs.* 23.8% of patients ($p<0.001$). The Genant-modified Sharp score progressed by 2.32 in the placebo group and 1.21 in the abatacept group (significance not stated).

Conclusion

In all trials comparing the respective monotherapies head to head MTX turned out to be as effective as the highly acclaimed biologics. That result was not expected and therefore was very surprising for most experts. Even clinical remissions (according to the DAS definition) were seen in the same frequency as with biologics. That is remarkable knowing that the term “remission” had not been accepted so far as possible outcome with conventional DMARD treatment.

Negative change scores indicating radiological repair also occurred under MTX monotherapy although not as frequently as with combination treatment (10). Retardation of radiological progression is stronger with TNF inhibition, probably since TNF inhibitors directly reduce osteoclast activity in addition to their anti-inflammatory effect. However, the progression was small for all treatment groups in most trials and the differences – although significant – may be clinically irrelevant. For example, the mean progression after three years in the TEMPO trial was only 1.2% of the maximum total Sharp score (448 units) in the MTX group *versus* 0.4% in the etanercept group (0.4% *vs.* 0.13% per year). As shown in the probability plot (6) the proportion of patients with progression was approximately 20% with MTX and 15% with etanercept after three years (ITT analysis with LOCF) (see also the paper by Pincus in this issue).

Table III. Clinical and radiographic results in trials comparing MTX with biologics head to head.

ACR response of MTX vs. biologic							Radiologic progression with MTX vs. biologic			
Biologic	endpoint	ACR 20%	ACR 50%	signif.	DAS remission	Ref.	endpoint	Sharp units	sign	No score-increase
Etanercept ERA	12 mo	65/72	~45/~50 *	no	--	1, 2	6 mo	1.06/0.57	yes	--
							12 mo	1.59/1.06	no	--
							24 mo	3.2 /1.3	yes	51/63%
Etanercept TEMPO	12 mo	75/76	43 /48	no	13/16	4	12 mo	2.8/ 0.52	yes	
	36 mo	70/71	44 /46	no		6	36 mo	5.95/1.61	yes	51/61%
Adalimumab PREMIER							6 mo	3.5 /2.1		
	12 mo	63 /54	46 /41	no		8	12 mo	5.7 /3.0	yes	
	24 mo	56 /48	43 /37	no	25/25		24 mo	10.4/5.5	yes	34/45%
Golimumab	6 mo	~52 /54	29 /33	no	28/25	9	6 mo	--		--
Tocilizumab	6 mo	53 /70	33 /45	yes	33/45	13	6 mo	--		

Table IV. Clinical and radiographic response in trials comparing ongoing MTX plus placebo with MTX plus biologic.

ACR response (%) of MTX + placebo vs. MTX + biologic						Radiologic progression with MTX + placebo vs. MTX + biologic		
Biologic	endpoint	ACR 20	ACR 50	sign	Ref.	endpoint	Sharp units	sign
Infliximab		~ 25/~ 60	~ 9/~ 40	yes	10	12 mo	7.0 vs. 0.6	yes
CZP 200 mg/ 400 mg	6 mo	14/~ 60		yes	11	12 mo	2.8/ 0.2 – 0.4	yes
Anakinra	24 mo	22 vs. 38	8 vs. 17	yes	12	---	---	---
Rituximab	6 mo	18 vs. 51	5 vs. 27	yes	15	6 mo	1.2 vs. 0.6	no
Abatacept	12 mo	40 vs. 60	17 vs. 40	yes	16	12 mo	2.3 vs. 1.2	yes

Since all studies impressively indicated that the efficacy of biologics was significantly potentiated by combining them with MTX (the combination always performed better than the monotherapies), nowadays biologics are regularly combined with MTX in the treatment of RA.

Results of different trials cannot be compared directly. However, it appears that MTX performs slightly better than adalimumab (dosage problem?), is equal to etanercept and golimumab, but is significantly inferior to tocilizumab (Table III).

For several biologics a direct comparison with MTX does not exist. In those cases placebo or the biologic agent were added to an ongoing but inadequate MTX treatment. When interpreting the results of these trials one has to consider that all patients within the MTX and combination groups were incomplete responders to MTX. This may be “forgotten” to include when results of those trials are communicated. When the difference in efficacy between the MTX plus biologic group and the MTX plus placebo group is taken as an indi-

cator of the relative therapeutic power, there appears to be an order of efficacy from certolizumab (best) to infliximab, rituximab, abatacept, and anakinra (worst) (Table IV).

In general, improvement started much earlier with biologic treatment than with MTX treatment. This may be related to the different mechanisms of action and a psychotropic effect of TNF inhibitors. In addition, the initial dose of MTX was too low and was escalated only slowly, in some trials merely “if needed”.

In most studies comparing both monotherapies the dropout rates within the MTX groups was higher than in the biologic groups. This may have negatively influenced the efficacy results using the ITT analysis with LOCF: the time under medication and for clinical improvement is shorter in withdrawals than in completers. A similar problem is that the rate of radiological progression until withdrawal was projected up to the end of the study (*i.e.* 12, 24, 36 mo) in a linear way. This is incorrect since many previous studies have shown that radiographic progression

with conventional DMARD treatment (including MTX) is stronger inhibited with time.

Furthermore, folic acid supplementation may have hidden the real therapeutic potential of MTX (17, 18).

In summary, comparative trials with biologics have confirmed MTX as a very effective DMARD. However, there are indications to suspect that the efficacy of MTX is still underestimated in clinical trials and, as a consequence, in clinical practice.

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