CHAPTER 3

The BeSt story: on strategy trials in rheumatoid arthritis

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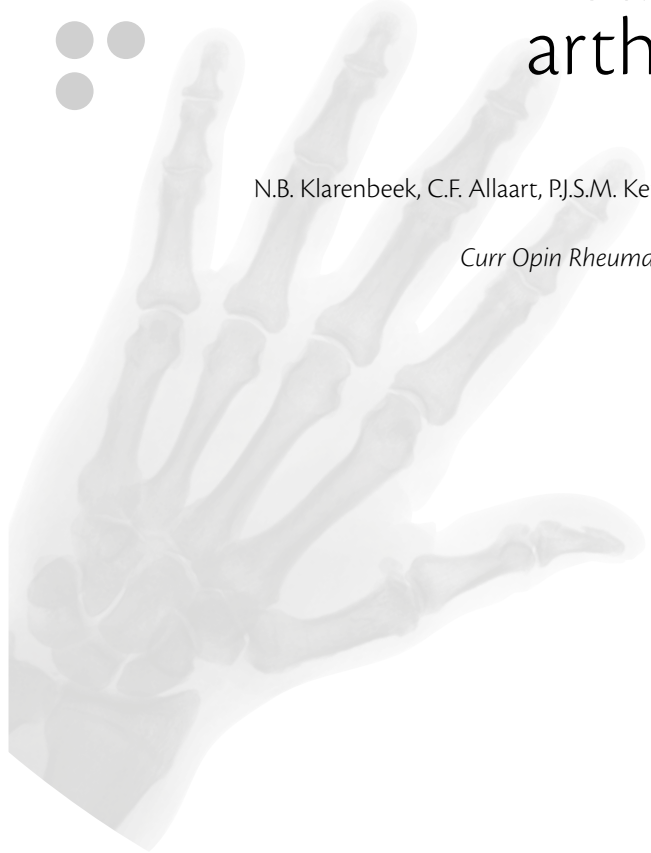

ABSTRACT

Purpose of review To give an overview of recent strategy trials for the treatment of rheumatoid arthritis (RA).

Recent findings Strategy studies showed a clear benefit of dynamic result-driven treatment towards tight control of disease activity compared with 'usual care' in RA-patients. In addition, treatment given after short symptom duration gives better outcomes than later initiation of treatment. In many trials, combination therapies, especially combinations with prednisolone or biologicals, were superior to monotherapies. Moreover, combination therapies were more effective if given early in the disease as compared with a delayed introduction, giving support to the window-of-opportunity hypothesis. In the BeSt study, initial combination therapy could be successfully discontinued in half of the patients, emphasising that 'initial' would mean 'temporary'. Less evidence is available about initial combination in comparison with combination therapy with a shorter delay. Larger tight-controlled, goal-steered, dynamic strategy trials comparing initial combination therapy with a short-delay combination therapy will help to translate the use of initial (temporary) combination therapy into normal daily practice.

Summary Treatment strategy trials have demonstrated that in the majority of patients with RA the following approach is the most beneficial: goal-steered, dynamic treatment towards tight control of disease activity, including early introduction of (an) effective disease-modifying antirheumatic drug(s) in combination with prednisone or anti-tumour necrosis factor, which includes tapering of the medication if remission or low disease activity is achieved.

INTRODUCTION

The treatment options for rheumatoid arthritis (RA) patients have increased substantially in the past few decades. New insights led to new treatment paradigms, including early introduction of treatment, the use of various combination therapies (including traditional disease-modifying antirheumatic drugs (DMARDs), biologicals, corticosteroids) and response-driven treatment, in which remission appears to be an attainable goal. There have been numerous trials with head-to-head comparisons of different (combinations of) drugs. However, extrapolation to clinical practice is usually difficult. Daily practice is much more dynamic than the regimens in comparative drug trials. Therefore, strategy trials have been published, in which the emphasis was not on the comparison of individual drugs but on the application of the available treatment options in a continuous, dynamic, 'real life' approach. In this review we discuss important lessons from those strategy trials, with a focus on new (follow-up) trials published during the last year.

Choosing optimal treatment

One of the important issues tackled in strategy trials is: what is the optimal way to use DMARDs in clinical practice? It is clear that RA-patients benefit from early introduction of DMARDs.[1,2] With the rising number of drugs available for the treatment for RA, numerous treatment sequences and combinations are possible. Comparative drug studies showed that initial combination therapy, including DMARDs with prednisolone or anti-tumour necrosis factor (anti-TNF) (but not combination therapy with conventional DMARDs alone[3]) gives earlier improvement and better outcomes than initial monotherapy in most patients.[4–10] However, it is not clear whether this is also the case in a dynamic strategy, whether there is an optimal timing of combination therapy and how dynamic treatment should be directed.

Recent (follow-up) studies comparing combinations of conventional DMARDs

The Combination Anti-Rheumatic Drugs in Early RA (CARDERA) trial[11] *(table 1)*, a randomised controlled trial (RCT) comparing methotrexate (MTX) + placebo with MTX along with prednisolone, ciclosporin or both, showed a significant reduction in the development of new erosions by adding either ciclosporin or prednisolone to MTX monotherapy. The lowest number of new erosions was seen with the combination of the three drugs.

During the second year of the Ciclosporin, Methotrexate, Steroid in RA (CIMESTRA) trial[12] *(table 2)* which had originally compared initial MTX monotherapy with a combination of MTX and ciclosporin, adding hydroxychloroquine (HCQ) to MTX monotherapy was compared to changing MTX and ciclosporin to MTX and HCQ. In both groups, patients were seen every 4 weeks with the absence of swollen joints as treatment goal. Individual swollen joints were injected with betamethason. After 2 years of treatment, the initial combination group continued to do better in terms of American College of

TABLE 1 Important new randomised controlled trials published between November 2007 and December 2008

	Patients			Treatment				Outcomes		
	n	Disease duration	Follow-up	Treatment groups	Placebo	Tight control	Result-driven	Clinical	Radiological	Toxicity
Verstappen et al. (CAMERA)	299	< 1 year	2 years	Intensive vs conventional strategy; all MTX step-up	No	Yes, monthly in intensive group	Yes, remission (computerized decision) in intensive group	Better AUCs for nearly all clinical variables (intensive vs conventional)	% with progression similar; if progression present: conventional arm ↑absolute level of progression	Slightly ↑AEs reported and AE related withdrawals in intensive group
Emery, et al. (COMET)	542	¼ - 2 years	1 year	MTX, MTX + ETA	Yes	No	No	↓HAQ, ↓DAS, ↑remission % (combination vs MTX)	↓progression (combination vs MTX)	No major differences
Choy, et al. (CARDERA)	467	< 2 years	2 years	MTX vs MTX + CSA (CSA after 3 months) vs MTX + step-down pred vs triple therapy	Yes	No	No	initially ↑ ACR20, 50 and 70 and DAS28 with triple therapy vs MTX, after 2 years no differences, ↓ HAQ with triple therapy and MTX + pred	↓erosions with all combinations, triple therapy least erosions	Pred: ↑ hypertension, ↓bone mineral density CSA: ↑ hypertension, mouth ulcers, headaches, transient creatinine elevations
Saunders, et al.	96	Symptom duration < 5 years	1 year	SSZ step up, SSZ + MTX + HCQ parallel (+dose increases)	No	Yes, monthly	Yes, DAS28 ≤3.2	No differences in DAS28, remission, ACR20, 50, 70 responses	No differences between the groups	No major differences
Van Tuyl, et al. (pilot)	21	< 3 months	40 weeks	All: SSZ + MTX +HCQ + high dose step-down pred,	No	Yes, after 8 and 21 weeks	Yes, DAS28 ≤3.2 or CTX-II ≤150	High ACR response rates and remission %, no differences between the groups	Not reported	4 treatment related low to moderate severe adverse events
Van Vollenhoven, et al. (SWEFOT, abstract)	487	Symptom duration < 1 year	1 year	All MTX, after 3 months DAS≥3.2 n=258 randomized: MTX + SSZ + HCQ vs MTX + IFX	No	No	Only at 3 months	↑ACR20, 50 and ↑EULAR good response, no difference in ACR70 response (MTX+IFX vs MTX, SSZ,HCQ)	Not reported	Not reported
Soubrier, et al. (Guepard, abstract)	65	< 6 months	1 year	MTX step-up (ADA added if DAS28 > 3.2) vs MTX + ADA parallel	No	Yes, three-monthly	Yes, DAS28 < 3.2	At wk 12 ↓ AUC DAS28, ↑ %DAS28 < 3.2. After 1 year no differences. IFX use similar. (initial combi vs MTX)	No differences	Not reported
Leirisalo-Repo et al (NEO-RACo, abstract)	100	Symptom duration < 1 year	2 year	FINRACo vs FINRACo + 5 gifts IFX; (FIN-RACo: MTX + SSZ + HCQ + pred)	Yes	No	Yes, remission	↑remission %, no difference in sustained remission (IFX vs placebo)	↓progression (IFX vs placebo)	Not reported
Van Eijk, et al (STReam, abstract)	82	Symptom duration < 2 years	1 year	Step-up aiming at remission vs conventional treatment	No	Yes, three-monthly (intensive group)	Yes, remission (intensive group)	No differences in DAS, HAQ, remission rates	No differences	No medication related serious adverse events in both groups

MTX, methotrexate; CSA, ciclosporin A; HCQ, hydroxychloroquine; SSZ, sulfasalazine; pred, prednisolone; ETA, etanercept; ADA, adalimumab; IFX, infliximab; HAQ, health assessment questionnaire DAS28, disease activity score in 28 joints; AUC, area-under-the-curve, ACR, American College of Rheumatology; EULAR, European League against Rheumatism; AEs, adverse events

TABLE 2 Interesting follow-up studies of randomised controlled trials published or presented between November 2007 and December 2008

	Patients			Treatment				Outcomes		
	n	Disease duration	Follow-up	Treatment groups	Placebo	Tight control	Result-driven	Clinical	Radiological	Toxicity
Van der Kooij, et al. (BeSt)	508	≤ 2 years	4 years	Sequential monotherapy vs step-up combination therapy vs initial combi SSZ + MTX + pred vs initial combi MTX + IFX	No	Yes, three-monthly	Yes, DAS <2.4	Earlier improvement in DAS, HAQ, remission % (initial combi vs initial monotherapy), after 2 years no differences, drug-free remission 8-18%	↓progression initial combi vs initial monotherapy	No major differences
Van der Heijde, et al. (TEMPO)	682	½ - 20 years	3 years	MTX, ETA, MTX + ETA	Yes	No	No	↓HAQ, ↓DAS, ↑ACR responses, ↑remission %, with combination vs both monotherapies	↓progression with ETA and MTX + ETA than MTX	No major differences
Hetland, et al. (CIMESTRA)	160	< 6 months	2 years	MTX, MTX + CSA; i.a. bethamethason in swollen joints, HCQ added week 68, both arms step-up	Yes	Yes, monthly	Yes, ACR20, absence swollen joints	↑ACR20 and 50, no differences in remission % and HAQ (combination vs mono)	No differences between the groups	Combination ↑transient creatinine elevations, effect RR unclear
Rantalaiho, et al. (FIN-RACo, abstract)	195	Symptom duration < 2 years	11 years	SSZ vs MTX + SSZ + HCQ + pred, after 2 years no treatment protocol	No	No	Yes, remission	Initial: better clinical response, after 5 years: slightly ↑ remission and ↓DAS28 (combination vs monotherapy), not reported in abstract	↓progression after 11 years in combination group	After 2 years: no major differences; later: not reported
Van Tuyl, et al. (COBRA, abstract)	155	< 2 years	11 years	Initial: SSZ vs MTX + SSZ + step-down pred, after 56 weeks no treatment protocol	No	No	No	Initial: better clinical response in combination group, after 5 years no difference HAQ and DAS28, not reported in abstract	↓progression until 5 years in combination group, after 11 years: no significant differences	↓withdrawals in combination group

MTX, methotrexate; CSA, ciclosporin A; HCQ, hydroxychloroquine; SSZ, sulfasalazine; pred, prednisolone; ETA, etanercept; IFX, infliximab; HAQ, health assessment questionnaire; DAS: disease activity score in 44 joints; DAS28, disease activity score in 28 joints, ACR, American College of Rheumatology

Rheumatology (ACR) responses than the initial monotherapy group. As expected, the percentages of patients achieving ACR remission were not significantly different (41% vs 35%) between the two groups nor were the outcomes in functional ability (health assessment questionnaire (HAQ) score 0 vs 0.1) and in radiological progression from baseline to 2 years.

The Combinatietherapie bij Reumatoïde Artritis (COBRA) trial[6,13] was the first to explore the possibility of a step-down approach in treatment of RA. The combination MTX, sulfasalazine (SSZ) and a rapidly tapered high dose of prednisolone was more effective than SSZ alone, with a better clinical response and significantly less joint damage progression until 5 years of follow-up. A recent update on radiological progression rates after 11 years showed no longer a significant difference between the initial combination group and the initial monotherapy group, possibly because of the unequal dropout rates in both groups.[14]

The Finnish Rheumatoid Arthritis Combination therapy (FIN-RACo) trial[7] showed that in patients with recent-onset RA combination therapy (SSZ, MTX, HCQ and prednisolone) is superior to SSZ monotherapy with significantly higher remission rates, less radiological damage and comparable toxicity, while aiming at remission. After 11 years of dynamic, remission-steered treatment, the initial combination group still had less radiological progression compared to the initial monotherapy group (p=0.04).[15]

The BeSt study[16,17] is a randomised controlled trial in which four different, DAS-steered, dynamic (including tapering to drug free remission) treatment strategies are compared. Two groups (group 1, sequential monotherapy, and group 2, step-up combination therapy) started with MTX monotherapy with introduction of combination therapy with infliximab or prednisolone in case of insufficient response to at least three conventional DMARDs. The other two groups (group 3, initial combination therapy with MTX, SSZ and prednisolone, and group 4, initial combination therapy with MTX and infliximab). The initial combination therapy groups showed an earlier improvement in DAS, HAQ and quality of life,[18] earlier remission, and less radiological progression compared to the initial monotherapy groups. The dynamic study design aiming at a DAS 2.4 or less resulted in comparable results in functional ability in the four treatment groups from the end of the first year of treatment onwards, meanwhile enabling most patients in the initial combination therapy groups to taper their medication, and most patients in the initial monotherapy groups to increase or change their medication. Despite only a brief period of clinical differences in response early in the trial between the treatment arms, patients treated with initial combination therapy still had significantly less joint damage progression after 5 years as compared with the initial monotherapy groups. After 5 years, 48% of patients are in clinical remission, defined as a DAS <1.6.[19] Fourteen, 16, 10 and 19% of patients had by then successfully discontinued all antirheumatic drugs. The patients in sustained drug-free remission (>1 year) barely showed radiological progression after the discontinuation of DMARDs.

Saunders, et al.[20] compared initial combination therapy with conventional DMARDs (SSZ, MTX and HCQ) to a step-up regimen starting with SSZ monotherapy and subsequent addition of MTX and HCQ. The aim was to achieve a DAS28<3.2 at 3-monthly visits, inducing dose increases in both arms. There is no mention of tapering. Sixty percent in the initial combination therapy arm and 41% in the step-up to combination arm achieved European League Against Rheumatism (EULAR) good response and 45 vs 33% achieved EULAR remission (p=NS, possibly because of small numbers) after 1 year of treatment. Radiological damage progression after 1 year was 6.0 $\pm$ 5.3 in the step-up group and 6.6 $\pm$ 7.0 in the initial combination group (p=NS), which can in part be explained by the high erosion scores at baseline and the chronological reading of radiographs, but may also reflect the absence of corticosteroids and biologicals in the two strategies.

Verschueren, et al[21] compared a DAS-guided step-down treatment strategy with conventional DMARDs with a step-up strategy in recent-onset RA patients in daily practice. The treating physician determined which approach would be taken. The majority of patients (52 versus 19) were treated according to the step-up approach. With the restriction that, precisely because of this study design, the groups are difficult to compare, the results showed earlier improvement, fewer side effects and fewer treatment failures in the step-down group than in the step-up group. These findings are in accordance with findings of the COBRA and the BeSt trials.

In conclusion, recent (strategy) trials confirmed the beneficial effect of early combination therapy with conventional DMARDs, including prednisolone, in comparison with monotherapy.

Recent (follow-up) trials comparing combinations with biologicals

With the use of biologicals, the treatment of RA has changed considerably. Several trials confirmed that combination therapy with any of the available anti-TNF inhibitors and MTX led to better clinical responses, functional improvement, quality of life and less radiological damage progression compared to treatment with MTX and anti-TNF therapy alone.[4] In patients with established RA the 3-years results of the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) trial[22] showed that patients treated with a combination of etanercept and MTX had significantly better DAS, higher remission rates and more improvement in HAQ scores compared with patients treated with either drug alone. Treatment with etanercept, alone or with MTX combined, led to less radiological damage progression than treatment with methotrexate monotherapy. In patients with recent-onset RA, the Combination Of Methotrexate and Etanercept Trial (COMET)[23] showed a comparable beneficial effect of the combination of MTX and etanercept over treatment with MTX alone. Fifty percent of the patients treated with combination therapy achieved clinical remission compared to 28% of patients treated with methotrexate alone (p<0.0001). Eighty percent and 59%, respectively, achieved radiographic non-progression (p<0.0001).

In the dynamic NEO-RACo trial,[24] the original FIN-RACo combination therapy (MTX-+SSZ+HCQ+prednisolone) and 5 doses of infliximab in the first 6 months of treatment was compared with the same combination with placebo. The aim was to achieve ACR

remission. The addition of infliximab resulted in significantly higher remission rates (70% versus 53%) and significantly less radiological joint damage progression after 2 years (-0.2 versus 1.4).
Following the introduction of anti-TNF, several biologicals with different immunological targets are developed. Abatacept and tocilizumab are approved as therapies for patients with rheumatoid arthritis, as was rituximab, previously used in the treatment of hematological malignancies. In most countries, reimbursement policies have made these drugs available only for patients who have failed on anti-TNF therapy.
The newer biologicals were individually evaluated as add-on vs methotrexate (or sometimes other DMARDs) treatment. Only tocilizumab (anti-IL6) was compared as monotherapy against MTX monotherapy in a parallel design in MTX-naïve patients and was more effective than MTX monotherapy in ACR 20, 50 and 70 responses and DAS28 remission.[25] The effect on radiological progression remains to be determined. Other new candidate treatments need to be evaluated. No conclusions can be made about long-term safety of the new biologicals.

Minimal delayed combination versus initial combination

The progression of time without effective treatment impairs functioning of RA-patients, and therefore needs to be shortened. The results of the BeSt study show that a delay of 6 to 9 months in clinical improvement, because of unsuccessful sequential or add-on treatment with conventional DMARDs, results in significantly more joint damage progression compared with patients treated with initial combination therapy.[26] This suggests that with delayed introduction of combination therapy the window of opportunity can be missed. Also, delayed infliximab could be less often discontinued than if employed as initial treatment.
Although on the group level, initial combination therapy leads to better outcomes than delayed therapy, a part of the RA population responds well to MTX monotherapy. Unfortunately, at this time it is not possible to predict who will respond to MTX alone. Therefore, an approach with a short period of MTX monotherapy, followed by immediate introduction of combination therapy in case of insufficient response might be appropriate. This approach was used in the SWEFOT trial[27] in which 487 recent-onset RA patients started with MTX monotherapy. If the DAS28 was at least 3.2 after 3-4 months, patients were randomised to either adding SSZ and HCQ to MTX (n=130) or adding infliximab to MTX (n=128). Unfortunately, the trial design does not allow us to compare this strategy to initial combination therapy. However, SWEFOT demonstrated that following failure on MTX monotherapy, patients who received infliximab added to MTX had significantly higher remission rates (42% versus 26%) and higher ACR50 and 70 responses (29% and 13%, 16% and 8%, respectively) after 1 year than patient who received the combination of conventional DMARDs.
The GUEPARD trial[28] presents a parallel comparison between initial MTX monotherapy (32 patients) and initial combination therapy with MTX + adalimumab (33 patients). If after 3 months, DAS28 was more than 3.2, adalimumab was added to MTX monotherapy or

increased in the combination arm, whereas medication would be tapered and stopped if the DAS28 was 3.2 or less. As expected, patients treated with initial MTX and adalimumab combination therapy showed an earlier improvement in disease activity than patients treated with initial MTX monotherapy, with 64% versus 25% of patients achieving a low disease activity at 12 weeks (p=0.001). Because of the dynamic treatment protocol, after 1 year, the proportion of patients with low disease activity was similar in both groups (65% versus 64%, p=0.98) and there were no differences in joint damage progression among the (small) groups. Interestingly, the total use of adalimumab did not differ between the groups. For a patient, a delay in clinical improvement of 3 months or more would be relevant, leading to the suggestion that initial anti-TNF therapy may be the best option.
In STRategies in Early Arthritis Management (STREAM), a study in relatively mild RA patients,[29] remission-steered treatment with initial MTX monotherapy followed by addition of anti-TNF was compared to 'conventional DMARD treatment'. In both groups, high remission rates, good clinical responses and less radiological damage were seen, without significant differences. This might be due to relatively low patient numbers, due to the patient profiles or both.

How to decide when to change medication?

With the introduction of superior (combinations of) drugs to suppress disease activity, the approach to treatment decisions has also changed. A rapid reduction in the number of inflamed joints and in erythrocyte sedimentation rate and C-reactive protein is now achievable. The TIght COntrol for Rheumatoid Arthritis (TICORA) trial showed that better disease control is possible with disease activity driven treatment than with observational therapy decisions,[30] with significantly lower disease activity, higher proportions of patients with a good response, higher remission rates and less radiological damage compared to the conventional-treated patients. The Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) trial[31] confirmed that tight-controlled treatment with a clear treatment goal is better than 'traditional' treatment. In this trial, decisions in the intensive arm were made based on a computerised decision program. The intensive treatment group showed significantly higher remission rates than the conventional treatment group (50% versus 37%, p=0.03) together with a higher turnover from low-dose MTX monotherapy to high-dose and combination therapy. In contrast to the TICORA trial, there was no clear difference in radiological progression between the two groups after 2-year follow-up.
The BeSt study showed that, with continuous steering at low disease activity, a comparable disease state can be achieved in all four groups, independent of initial treatment. The time to achieve low disease activity is longer in the initial monotherapy groups compared to the initial combination groups.[16,32] Therefore, fewer treatment adjustments are needed when treatment starts with initial combination therapy. Post-hoc comparative studies of the results of the BeSt study with the conventionally treated RA patients from two Dutch Early Arthritis Cohorts also showed a clinical benefit of DAS-steered treatment.[33]
In retrospect, it seems obvious that, regardless of the medication used, adjusting the medication in order to achieve a certain goal will lead to patients achieving that goal.

Only the time of achievement may differ with the strategy. The next questions are: what goal should we aim at and how 'tight' should tight control be?
As discussed, a number of trials implemented the concept of tight control in their protocol, but no large trials compared different treatment goals. Van Tuyl, et al.[34] did a small (pilot) trial comparing treatment steered at achieving a low disease activity (DAS28≤3.2) or at achieving a low C-terminal cross-linking of type II (CTX-II) level (marker for cartilage degradation, ≤150 nmol/mmol). Twenty-one patients were randomised and treated with the same medication, starting with a combination of SSZ, MTX, HCQ and a tapered high dose of prednisolone. After 40 weeks, 19 of 21 patients were in remission (DAS28 ≤2.6). Because of the limited patient number, no conclusions could be drawn on the usefulness of CTX-II in treatment decisions. Following FIN-RACo and NEO-RACo trials, the Dutch Rheumatoid Arthritis Monitoring Registry (DREAM) remission induction cohort has shown that in daily practice, a tight-controlled, DAS28 less than 2.6-steered, initial MTX monotherapy-based treatment strategy results in a high percentage of patients progressing to combination therapy as well as a high percentage (51%) achieving remission after 1 year.[35]
These results show that clinical remission seems to be an attainable goal. In general it is reasonable to expect that, if treatment is aimed at a lower level of disease activity, less loss of functioning and less joint damage will be observed, and more treatment adjustments in more patients. The frequency of controls will depend mostly on local logistics.

Translation to clinical practice

The most important consequence to draw from the strategy trials described in this review is that result-driven treatment is better than what used to be routine, 'observational' care. Frequent visits to the outpatient clinic with treatment adjustments based on specific, validated tools are necessary to reach the predefined goal as soon as possible. And it seems reasonable to steer at achieving remission.
Many trials have demonstrated that immediate suppression of disease activity leads to earlier clinical improvement and less joint damage progression, and that, on the group level, combination therapy is superior to treatment with DMARD monotherapy, without a clear negative effect on toxicity *(table 1 and 2)*. The BeSt trial, integrating tight control with DAS-steered therapy decisions while comparing four different treatment strategies where various combinations of various drugs were introduced at various times in the treatment of patients with recent-onset RA, probably comes closest to mimicking modern daily practice in a clinical trial.
The implementation into daily practice is a slowly going process. Regrettably, the benefits of early aggressive treatment vs the risk of overtreatment prevent rapid implementation in individual patients. Ideally, treatment is tailored for each patient separately, based on clinical characteristics, laboratory markers or both. Unfortunately, the correct prediction whether a patient will respond well to a certain therapy turns out to be difficult. Ongoing research will contribute to the understanding of the pathogenesis of RA and improve prediction models by, ideally, identification of new biomarkers.

Until accurate prediction is possible, the risk of undertreatment (loss of function, joint damage progression) versus the risk of overtreatment (toxicity) needs to be considered. Other barriers for the implementation of early combination therapy involve cost issues and concerns about safety of the newest drugs. In addition, some combinations are found complex to administer.[36] Given the evidence from various trials, it is reasonable to expect most patients to benefit most from initial treatment with a combination of drugs, including either prednisolone or a TNF-blocker. When the goal is achieved, the possibility of overtreatment should be anticipated by using a flexible protocol, which allows tapering and discontinuation of medication in a tight-controlled setting.
New research is needed to go further. The continuous search for biomarkers of disease stage and predictors of treatment response is essential to proceed to more individually tailored treatment in the future. Given their obvious potential, the newer biologicals need to be studied earlier in the disease course in comparison with established treatment strategies. Various treatment strategies should be compared, with no or with minimal treatment delay, looking at the induction of drug-free clinical and radiological remission, safety and total societal costs. It has to be confirmed that implementing the results of such studies into daily practice is possible and to the benefit of RA patients.

Conclusion

From various trials, including the BeSt study, the following aspects of RA treatment turn out to be beneficial:

1 early introduction of effective treatment with minimal delay in introduction of combination therapy including prednisolone or TNF blockers;
2 result-driven (for instance DAS ≤2.4 or remission) treatment;
3 tight controlled (based on measurement of disease activity) treatment

These three aspects should be and are being implemented in the treatment of recent-onset RA patients. New trials will help to fine tune the timing of the most effective drugs, which include the newer biologicals.

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