Combination therapy in rheumatoid arthritis: always the best option?

One of the major developments in the treatment of rheumatoid arthritis over the last decade and a half has been the realization that early and aggressive treatment leads to better outcomes for most patients. Early use of methotrexate and switching to a combination treatment regimen within the first 3–6 months if there is inadequate response to methotrexate is the currently accepted paradigm for rheumatoid arthritis treatment. To achieve better outcomes it is not enough to just use combination treatments; disease activity also needs to be measured and monitored with a 'treat-to-target' approach, where remission or low disease activity is the target and available medications are used either alone or in combination to get there.

KEYWORDS: combination treatment ■ remission ■ treat to target

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Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that is characterized by pain, swelling and stiffness leading to joint destruction, deformity and functional disability. Over the last decade, there have been major changes in the treatment of RA, resulting in better patient outcomes. Traditional disease-modifying antirheumatic drugs (DMARDs) in combination with TNF-α drugs and other biological agents, such as rituximab, abatacept and tocilizumab, lead to improved outcomes compared with traditional monotherapy treatment. In addition, realization that aggressive early treatment with methotrexate (MTX) and disease activity monitoring with treating to a target of remission or low disease activity has led to improved outcomes. In this article, we will discuss data about different combination therapies and their effectiveness in treating RA.

Remission

One of the major changes to the way we treat RA has been the adoption of 'treating-to-target' paradigm; where a composite disease activity index is used as a score to target with our therapies. Not only do we aim for lower scores, but now we can realistically talk about remission and, if not, at least low disease activity as a possible outcome for a lot of patients.

The current ACR- and European League Against Rheumatism (EULAR)-approved definition of remission is an absence of articular and extra-articular inflammation and disease activity [1]. To standardize the remission measure, the ACR and EULAR redefined remission in RA to find a uniform definition to be used in trials and clinical practice.

Two definitions of remission have been proposed: the Boolean-based definition includes four of the core set measures, and when scores of the tender joint count, swollen joint count, C-reactive protein (CRP; in mg/dl) and patient global assessment (0–10-point scale) are all in total ≤1, the patient is considered to be in remission. The second definition is a score less than or equal to 3.3 on the Simplified Disease Activity Index (SDAI).

The ACR/EULAR committee tested the validity of these definitions and saw that patients whose RA was in remission by several of the Boolean candidate definitions, as well as by the traditional SDAI definition (≤3.3), had an increased likelihood of radiographic stability during the subsequent year. Being in remission by any of the definitions increased the likelihood of stability on health assessment questionnaire scores, without important differences between definitions. The disease activity score in 28 joints (DAS28) definition, either at the traditional cut point (<2.6) or at a more stringent cut point (<2.0) was not as good as the other definitions. It was determined that the inclusion of ankles and forefeet are not required in the assessment of remission, but it is recommended that these joints are also included in the examination. Investigators should always report which joints were examined [2].

Disease activity measures

The disease activity score (DAS) was initially developed in order to measure disease activity

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as a single composite index. DAS44 was used in the beginning which measured four variables: Ritchie Tender Joint Index, number of swollen joints, acute-phase reactant (erythrocyte sedimentation rate [ESR] or CRP), and a general health score on a 100 mm Visual Analog Scale. If a patient's score was less than 1.6, it was considered to be remission. A newer, more time-efficient version of DAS in 28 joints (DAS28) was later developed as it was difficult for many rheumatologists to perform a 44 or greater joint count in clinical practice, with remission being a score less than 2.6. DAS28 requires evaluation of fewer joints; 28 compared with 44. However, the 28-joint count could lead to an underestimation of disease activity since the ankles and feet, which are commonly affected in RA patients, are not taken into account in this assessment.

Derivatives of the DAS have been created including SDAI and the Clinical Disease Activity Index (CDAI), which are less complex indices. SDAI includes five variables that are then added together: 28 tender joint count, 28 swollen joint count, CRP, and both a patient's and a physician's global disease activity assessment based on a 10 cm Visual Analog Scale, a score of less than 3.3 indicates remission. The CDAI is almost identical to SDAI, but it does not include CRP or an ESR. It is one of the few criteria that does not include a laboratory value; a score of 2.8 or below indicates remission. The advantage of these two assessments to the DAS is that they do not require a complex formula or calculator and can be used more readily in clinical practice. Studies performed using SDAI and CDAI suggest that remission scores are stringent and may more accurately reflect a state of decreased disease activity than DAS28 remission scores.

Routine Assessment of Patient Index Data 3 (RAPID3) is a composite index composed of three core data set measures on the multidimensional health assessment questionnaire, for function, pain and patient global estimate are each scored from 0–10, for the total score of 0–30. The severity categories are defined as high: >12; moderate: 6.01–12; low: 3.01–6.01; and near remission: ≤3 [3]. RAPID3 provides similar information to the DAS28 and SDAI/CDAI and can be calculated in 5–10 s. Most patients who met criteria for each of these four disease severity categories according to RAPID3 scores were found to meet similar activity categories for DAS28 and CDAI [4].

Treatment of RA

Since there is no cure for RA, remission has become the accepted treatment goal for RA patients. Clinical trials show that both early and established RA have demonstrated better remission rates and radiographic progression with early intensive treatment than monotherapy or routine care (Table 1) [5]. Treatment with synthetic DMARDs, as MTX the agent of choice, should be started within the first 3 months for patients with confirmed diagnosis and active disease. DMARDs alone do not control disease severity, prevent bone and cartilage damage or maintain the quality of life in a considerable proportion of RA patients. Approximately 40–50% of RA patients who receive MTX are adequately treated with only MTX and low-dose prednisone combination [6].

Sulfasalazine and hydroxychloroquine are reserved for patients unable to take MTX. Studies have shown benefits for RA patients with relatively low toxicity, as well as improvements in pain and function, within 4 weeks of treatment. They have been shown to slow radiographic progression after 1–3 years of therapy. They are considered to be a less potent DMARD and are typically used as part of a combination regimen.

Leflunomide, which is an immunoregulator of T lymphocyte proliferation, is comparable in efficacy to MTX; however, it is mostly used in place of MTX in combination with other DMARDs or biological DMARDs when side effects of MTX limit its use.

Biological treatments can also be used in combination to DMARDs in order to achieve remission. There are many different biological options including five TNF-α inhibitors, and abatacept, rituximab and tocilizumab as agents with different modes of action. ACR and EULAR limit recommendations for addition of a biologic to patients with high disease activity and poor prognosis in whom the DMARD treatment goal was not achieved and to DMARD-naive patients with poor prognostic factors. TNF- α inhibitors are the most commonly used biological agents; however, any biologic with similar data in similar patient types can be used as a first-line biologic. Currently abatacept and rituximab have data similar to TNF inhibitors and can be considered first-line biologics.

Different approaches to treatment

There are many different approaches to treatment a physician may decide to take, consisting of monotherapy, step-up therapy or combination therapy. Response to DMARD monotherapy is frequently suboptimal and patients with severe RA treated with MTX often only exhibit partial improvement [7]. MTX is most often the

Table 1. Clinical trials of tight control in early rheumatoid arthritis.

Study (year)	Duration of RA	Interventions/ groups	Patients (n)	Initial treatment	Timing and criteria for treatment adjustment	Conclusion	Ref.
TICORA (2004)	<5 years	Routine care	55	Monotherapy DMARD, combination therapy, triple therapy or alternative DMARD	3 months (DAS)	Intensive outpatient management of RA substantially improves disease activity, radiographic disease progression, physical function and quality of life	[8]
		Intensive therapy	55		Monthly (DAS)		
FIN-RACo (1999)	<2 years	Combination therapy	97	SSZ, MTX, HCQ, prednisone	3 months (variable)	Combination therapy more effective than monotherapy	[14]
BeSt (2005)	<2 years	Sequential monotherapy	126	MTX	3 months (DAS44)	Initial combination therapy with either infliximab or prednisone was the most effective strategy	[15]
		Step-up combination	121	MTX	3 months (DAS44)		
		Initial combination therapy plus high-dose prednisone	133	MTX, SSZ, prednisone	3 months (DAS44)		
		Initial combination therapy plus infliximab	128	MTX, infliximab	3 months (DAS44)		
CAMERA (2007)	<1 year	Intensive treatment	151	MTX dosage tailored to patient using computerized decision process	Monthly	Patients in the intensive strategy group were more likely to achieve one period of remission during the 2-year trial compared with the conventional strategy group	[10]
		Conventional treatment	148	MTX treated by common practices	3 months		
GUEPARD (2009)	<6 months	Monotherapy	32	MTX	3 months (DAS28)	Combination of MTX and ADA achieved a faster control of disease activity and led to lower DAS	[11]
		Combination therapy	33	MTX plus ADA			
SWEFOT (2009)	<1 year	Part 1: monotherapy	130	MTX	3 months	The addition of a biological agent to MTX monotherapy is more effective than combination therapy of traditional DMARDs	[13]
		Part 2: combination therapy	130	SSZ plus HCQ	12 months		
			128	Infliximab			

ADA: Adalimumab; DAS: Disease activity score; DAS28: Disease activity score in 28 joints; DAS44: Disease activity score in 44 joints; DMARD: Disease-modifying antirheumatic drug; HCQ: Hydroxychloroquine; MTX: Methotrexate; RA: Rheumatoid arthritis; SSZ: Sulfasalazine.

DMARD of choice for RA and should be used, when appropriate, as soon as possible. Monotherapy has been shown to decrease inflammation and slow radiographic progress, but the degree to which this is accomplished is variable. The earlier a treatment can be initiated, the better the overall outcome for clinical improvement and prevention of erosive disease.

Benefits of combination therapy

The TICORA study was the first of its kind in what we call strategy/treat-to-target trials. It was a single-blind, randomized controlled trial in Scotland. Patients were randomly assigned to either intensive or routine management. In the intensive treatment groups, treatment decisions to escalate therapy were based on the DAS score. In the routine care group, treatment changes were left up to the treating physician and there were no DAS-driven treatment escalations [8].

Results showed that mean fall in DAS was greater in the intensive group than in the routine group; patients treated intensively were more likely to have a good response or be in remission. Tight control of disease activity improved medium-term patient-centered outcomes. ACR20, 50 and 70 scores, as well as the radiographic scores, were also significantly better in the intensive treatment groups [8].

The FIN-RACo study demonstrated that combination DMARD therapy was more effective than monotherapy at inducing remission

in patients with early RA [3]. DMARD-naive patients with early RA received sulfasalazine with or without prednisone or combination therapy with sulfasalazine, MTX, hydroxychloroquine and prednisone. Patients were also stratified according to whether DMARDs were started <4 months (early) or >4 months (delayed) after symptom onset. After 2 years, remission rates were significantly lower in the delayed monotherapy group compared with the early monotherapy group. Among those receiving combination therapy, similar rates of remission were observed between the early and delayed treatment groups, and the rates were dramatically higher than those in delayed monotherapy. A total of 20% of patients on monotherapy and 42% on combination therapy achieved modified ACR remission at 2 years and this was sustained (remission at 6, 12 and 24 months) in 3 and 14% of patients, respectively. The rate of DAS28-defined remission was also higher among patients receiving combination therapy compared with patients receiving monotherapy (68 vs 41%, respectively) as was the proportion of patients with sustained DAS28 remission (37 and 6% of patients, respectively) [9].

The BeSt (a Dutch acronym for treatment strategies) trial compared early and late initiation of treatment with infliximab plus MTX and found that after 3 years of treatment, patients initially treated with the combination of infliximab plus MTX, had more functional improvement, measured by the health assessment questionnaire, and had less radiographic progression compared with those who switched to infliximab after failing other therapies at 1 year. The 2-year results showed that it did not make a difference what strategy was used initially, as long as aggressive escalation of treatment was based on disease activity measurement, all patients had similar responses.

The CAMERA study investigated whether intensive treatment with MTX according to a strict protocol and a computerized decision program was more beneficial compared with the conventional treatment with MTX in early RA patients. In this 2-year randomized, open-label trial, 299 patients with early RA were randomly assigned to the intensive strategy group or the conventional strategy group. Patients in the intensive treatment group visited the outpatient clinics once every month, the MTX dosage was tailored to the individual on the basis of predefined response criteria, using a computerized decision program. Patients in the conventional treatment strategy came to the outpatient clinic once every 3 months and were treated according to common practice. In total, 50% of the patients in the intensive strategy group achieved at least one period of remission during the 2-year trial in comparison to the 37% in the conventional strategy group. This shows the clinical efficacy early in the course of the disease by intensifying treatment with MTX aiming for remission by tailoring to the individual patient [10].

GUEPARD was an open randomized clinical trial which had two aims. The first was to determine if 3 months of adalimumab (ADA) in association with MTX could achieve and maintain low disease activity (DAS28 under 3.2) in patients with early and active RA compared with MTX alone. The second was to determine if ADA could be added to MTX only patients after 3 months and whether similar outcomes could be achieved at 1 year, even after the 3-month delay in starting the combination. Patients had on average approximately 6 months of disease and were grouped into two arms: MTX monotherapy and initial combination therapy with MTX and ADA. The decision to adjust medication was made every 3 months on the basis of the DAS28. If the patients did not achieve a low DAS the physician adjusted therapy by proceeding to the next step in the allocated treatment group.

At the end of the trial initial combination therapy resulted in statistically lower median area under the curve in the first 12 weeks compared with monotherapy for tender joint count ($p = 0.0071$), swollen joint count ($p = 0.0004$) and ESR ($p = 0.0014$), but not for patients' global assessment ($p = 0.13$). Physician overall assessment ($p = 0.0017$) improved significantly in the initial combination therapy in the first 12 weeks, but there was no difference in pain, fatigue or CRP. MTX anti-TNF combination therapy, given initially and then as required, produced a faster response. It did not achieve a better subsequent (1 year) clinical or radiological outcome than a 3-month delayed initiation of anti-TNF in patients who still had active disease despite MTX therapy [11].

In the GUEPARD study, the faster response of DAS for the initial combination group of MTX and ADA versus MTX only, resulted in a higher DAS area under the curve for the latter. However, unique in this study was the quick addition of ADA to MTX after only 3 months if the target was not reached, this led to similar functional and radiological outcomes in both groups [12].

Finally, the SWEFOT trial provides more data that, compared to a combination of traditional DMARDs, MTX plus a biologic agent combination may be more effective. In this study RA patients with less than 1 year of disease were all randomized to MTX at first for 3 months. After this period those who did not achieved low disease activity score were randomized to either DMARD combination/triple therapy with sulfalazine and hydroxycholoquine or combination of MTX with ADA. After 1 year, significantly more patients were better controlled in the biologic combination compared with triple therapy. After 2 years, statistical significance was lost, but numerically more patients were doing better with the biologic combination [13].

Conclusion

Currently available data suggest that treatment should be based on the tight control of disease to reach remission or low disease activity. Sometimes adding a biologic in combination with MTX is the best option we have for trying to achieve remission or low disease activity state in

Executive summary

Background

- Rheumatoid arthritis is a chronic autoimmune inflammatory disease characterized by pain, swelling and stiffness leading to joint destruction, deformity and functional disability.
- Traditional disease-modifying antirheumatic drugs in combination with biological agents lead to improved outcomes compared with traditional monotherapy treatment.
- Aggressive early treatment with methotrexate (MTX) and disease activity monitoring with treating to a target of remission or low disease activity has led to improved outcomes.

Remission

- The ACR- and European League Against Rheumatism-approved definition of remission is an absence of articular and extra-articular inflammation and disease activity.
- Two new definitions of remission:
  - The Boolean-based definition: scores on the tender joint count, swollen joint count, C-reactive protein (CRP; in mg/dl), and patient global assessment (0–10-point scale) are all ≤1 the patient is considered to be in remission.
  - A score less than or equal to 3.3 on the Simplified Disease Activity Index.

Disease activity measures

- Disease activity score: consisted of Ritchie Tender Joint Index, number of swollen joints, acute-phase reactant (erythrocyte sedimentation rate or CRP), and a general health score on a 100 mm Visual Analog Scale, <1.6 indicates remission. The disease activity score in 28 joints requires evaluation of fewer joints, <2.6 indicates remission. Simplified Disease Activity Index includes five variables, which are then added together: 28 tender joint count, 28 swollen joint count, CRP and both a patient's and a physician's global disease activity based on a 10 cm Visual Analog Scale, <3.3 indicates remission. Clinical Disease Activity Index identical to Simplified Disease Activity Index, but does not include CRP, <2.8 indicates remission. Routine Assessment of Patient Index Data 3 composed of three core data set measures on the multidimensional health assessment questionnaire, for function, pain and patient global estimate are each scored from 0–10, combining together for the total score of 0–30 (high: >12; moderate: 6.01–12; low: 3.01–6.01; and near remission: ≤3).

Different approaches to treatment

- Monotherapy is shown to decrease inflammation and show radiographic progress, but the degree to which this is accomplished is variable.
- The earlier a treatment can be initiated, the better the overall outcome for clinical improvement and prevention of erosive disease.

Benefits of combination therapy

- The TICORA study showed that intensive outpatient management of rheumatoid arthritis substantially improves disease activity, radiographic disease progression, physical function and quality of life.
- The FIN-RACo study showed that combination therapy is more effective than monotherapy.
- The BeSt study showed that initial combination therapy with either infliximab or prednisone was the most effective strategy.
- The CAMERA study showed that patients in the intensive strategy group were more likely to achieve one period of remission during the 2-year trial compared with the conventional strategy group.
- The GUEPARD study showed that combination of MTX and adalimumab achieved a faster control of disease activity and led to lower disease activity scores.
- The SWEFOT trial showed that MTX in addition to a biological agent is more effective than combination therapy with traditional disease-modifying antirheumatic drugs.

Conclusion

- After MTX, adding a biologic agent is the current standard of care for rheumatoid arthritis patients.
- Treatment should be based on the tight control of disease to reach remission or low disease activity.

most RA patients. The questions that remain are related to what to do with biologics when patients are in remission: do we stop them, decrease the dose and or frequency or continue as is? Is there a role for initial biologic combination before we try MTX? Further studies will help elucidate these and hopefully provide better and more relief to our patients.

Future perspective

Over the next 5–10 years, we will need to work on finding ways to reduce the time required to assess RA by rheumatologists. In addition to finding more effective predictive tools and improving currently available predictive tools in order to make the prediction of prognosis more accurate. We will need more data regarding what to do with biologics once patients are in remission – that is life-long treatment – or is it possible to achieve drug-free remission?

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