Clinical Rheumatology (2020) 39:1363–1368
https://doi.org/10.1007/s10067-020-05001-x

PERSPECTIVES IN RHEUMATOLOGY

Treatment strategies are more important than drugs in the management of rheumatoid arthritis

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Received: 22 January 2020 / Revised: 10 February 2020 / Accepted: 14 February 2020 / Published online: 22 February 2020

Abstract

The treatment of inflammatory arthritides has been changed dramatically in the past two decades with the introduction of the biological (b) disease-modifying anti-rheumatic drugs (DMARDs) as well as the targeting synthetic (ts) DMARDs that can be used as monotherapy or in combination with conventional synthetic (cs) DMARDs. The concept of treat to target (T2T) and tight control monitoring of disease activity represents a therapeutic paradigm of modern rheumatology. In rheumatoid arthritis (RA), this treatment approach has proven to be effective in many clinical trials and is now a well-established approach. The most common treatment strategies rely on the combination of csDMARDs (mainly methotrexate, sulfasalazine and hydroxychloroquine). This comes from different studies which compare the outcomes of combination therapies versus csDMARD monotherapy or versus methotrexate plus biologics in early RA patients. Here, we review the literature of the most important T2T studies for RA patients. The results showed that a tight control strategy appears to be more important than a specific drug to control RA. T2T approach aiming for remission or low disease activity can be achieved in early RA patients using less expensive drugs in comparison to newer drugs and this may need to be recognised in the future recommendations for the management of RA.

Key Points

- *Tight-control and treat-to-target (T2T) strategies are the cornerstone in achieving remission or low disease activity in rheumatoid arthritis (RA)*
- *A plethora of clinical trials has confirmed the efficacy of csDMARDs when the tight-control and T2T strategies are applied*
- *T2T and tight-control strategies are a less expensive option in comparison to newer drugs and may be recognised in the future recommendations for the management of RA.*
- *Treatment decisions and strategies are more important than just the drugs.*

Keywords bDMARDs · csDMARDs · RA · Tight control · Treat to target · tsDMARDs

Introduction

In the last two decades, better and more effective treatments are constantly being developed in the battle of treating inflammatory arthritides (IA). With the advent of biologic (b) disease-modifying anti-rheumatic drugs (DMARDs), the clinical outcomes for patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthropathies (AxSpA) have been dramatically improved. Recently, new drugs have been developed and approved for their clinical use by international regulating bodies [1]. As such, the targeting synthetic (ts) DMARDs like the Janus kinase (JAK) inhibitors interfering with the JAK-STAT signaling pathway, created a new DMARD category [1]. Finally, many biosimilars targeting the tumour necrosis factor (TNF) and one targeting the CD20 molecule on B cells are also available [1]. On the other hand, years ago, only some non-steroidal anti-inflammatory drugs (NSAIDs), a few conventional synthetic (cs) DMARDs such as methotrexate (MTX), sulfasalazine

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(SSZ), hydroxychloroquine (HCQ), gold salts and D-penicillamine were available for the treatment of RA [2, 3]. At that time, treatment initiation was delayed, based mainly on monotherapy schemes with csDMARDs or in combination with steroids. At that time, controlling disease activity was indeed a difficult task.

Nowadays, with such a plethora of cs-, ts-, bDMARDs and the biosimilars, have we reached to a point of being able to successfully treat RA and gain disease control? Are we able to achieve remission or low disease activity (LDA)? [4, 5]. The concept of treat to target (T2T) and tight control monitoring of disease activity represents a therapeutic paradigm of modern rheumatology. In RA, this treatment approach has proven to be effective in many clinical trials and remission or LDA are now possible. To this end, a literature review of the most important T2T and tight control studies aiming for remission or LDA in RA patients has been carried out and discussed appropriately trying to give answers to the above questions.

Treatment strategies

Over the past decades, most published randomised controlled trials (RCTs) regarding the management of IA and especially of RA have focused on the safety and efficacy of bDMARDs in comparison with csDMARDs. However, the most important information to be gathered from these RCTs is not only the comparison between those agents, but rather the chosen strategies of T2T and tight control aiming for remission or LDA. In this direction, treatment decisions and strategies are much more important than the drugs in sine, with the T2T strategy being the ideal approach [6]. This is because it focuses patient care on (a) setting targets for the therapeutic response, (b) applying shared decision-making with the patient, (c) tight control and monitoring disease activity and (d) allowing therapeutic adjustments when the desired target is not reached. The core elements of T2T approach have been incorporated into the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recommendations for RA, PsA and even for AxSpA [1].

The concept of T2T has been originally based on evidence from other chronic diseases such as diabetes mellitus (DM), hypertension and dyslipidemia [7]. The paradigm of DM is convincing since those patients manifest high rates of morbidity and mortality due to cardiovascular complications (CVCs). To avoid the above complications, physicians treat DM in a different manner than they used to do in the past. The target now is not only to normalise serum glucose, but to decrease the glycosylated haemoglobin below 6%, to normalise blood pressure levels (< 120/80 mmHg) and to decrease low-density lipoprotein (LDL) in less than 90 mg/dl [8]. With this T2T approach, physicians are now able to treat much better DM and minimise CVCs. In the same manner, patients suffering from RA should be treated using specific therapeutic targets, in order to achieve better outcomes as far as it concerns the disease in sine, but also several possible comorbidities. Nevertheless, this should be supported by data from RCTs demonstrating that T2T aggressive treatment approaches are more advantageous from the conventional treatment.

Early identification and treatment of RA is crucial in order to reduce structural damage progression and the burden of disability of this disorder. In the next section, an effort is made in this direction showing that an early and aggressive T2T treatment can bring fruitful results.

Treat to target and tight control monitoring disease activity

In the everyday clinical practice, an early RA intervention starts with MTX as the first choice csDMARD. MTX has shown a good safety and efficacy profile in terms of clinical improvement but also in terms of delaying radiographic progression. Additionally, MTX can be combined with other csDMARDs mostly HCQ and SSZ plus steroids. Thus, the most common treatment strategies rely on a csDMARD combination scheme [9, 10]. This comes from different studies which compare the effect of combination therapy with csDMARDs versus csDMARD monotherapy in early RA patients. To this end, investigators from the Netherlands designed the COmbinatie therapy Bij Rheumatoide Arthritis (COBRA) study. In this trial, MTX + SSZ plus high dose of prednisone (initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day) were compared to SSZ monotherapy. This study included 155 patients (76 received MTX + SSZ + high-dose prednisone and 79 SSZ only), and it was a double-blind randomised controlled trial in patients with early RA. The results showed that combination therapy was superior to SSZ monotherapy when it comes to clinical efficacy and has long-term structural integrity benefits in early RA patients [11, 12]. In addition, 11 years later, the same patients using the combination therapy scheme appeared to have lower mortality rates [13]. Finally, after 23 years of follow-up, patients in the combination therapy scheme had normalised mortality rates being similar to those of the general population [14]. The above study confirmed that an early and aggressive treatment approach has long-term beneficial effects, not only in terms of controlling disease activity, but also in terms of inhibiting the progression of structural damage and reducing morbidity and mortality.

In the past, remission was a rare phenomenon in rheumatology. However, it has been chosen as the treatment goal and primary endpoint in the combination therapy and tight control studies. The outcomes of these studies were based on the number of patients in remission using the disease activity

score for 28 joints (DAS28), or for 44 joints (DAS44) as well as the ACR clinical remission and good response according to EULAR criteria [15, 16]. Remission has been chosen as the treatment goal by the Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) study late in the 1990s for the first time. In this study, patients receiving csDMARDs in combination therapy (MTX + SSZ + HCQ plus prednisone) were in remission 2 years after baseline evaluation when compared with those taken monotherapy with SSZ + prednisone [17]. The results of the above study were stupendous due to the fact that sustained remission and reduced radiographic progression have been observed 11 years later with csDMARDs combination therapy being the reason [18]. In addition, investigators from the FIN-RACo trial showed that clinicians should aim for early intervention. A delay of instituting a therapy decreases the ability of traditional csDMARD monotherapy to induce remission as compared with the combination group receiving csDMARDs therapy in early RA patients [19]. Subsequently, another study was undertaken to determine whether infliximab (INF) added to patients in the FIN-RACo trial for the initial 6 months can improve the 2-year outcome. It was shown that patients in the FIN-RACo combination scheme achieved clinical remission and had minimal joint progression. The addition of INF delays the radiographic progression [20]. However, after 5 years of follow-up, no differences have been observed between groups after 6 months of treatment [21]. In addition, in a 10-year follow-up, the results have been maintained in most patients in the initial combination treatment regardless the INF infusions [22]. Finally, early RA intervention, as supported by the NEO-RACo trial, has the lowest rates of long-term treatment failure [23]. The above findings demonstrate that a tight control strategy appears to be more important rather than a specific drug to control RA. Fransen et al. reported the effectiveness of systematic monitoring of RA disease activity. He showed that systematic monitoring may lead to more changes in csDMARDs treatment and low disease activity in a large number of patients [24].

The importance of tight control strategy directed to T2T was subsequently confirmed by the Tight COntrol of Rheumatoid Arthritis (TICORA) study. The aim of this study was to compare tight control treatment with csDMARDs versus routine treatment. Results were again astonishing showing a remission rate of 65% using csDMARDs in the intensive management group [25]. The Behandel Strategieen (BeSt) study was a multicenter randomised clinical trial in patients with early RA. This study comprised four groups: (a) sequential monotherapy using MTX, (b) step-up combination therapy using csDMARDs, (c) initial combination therapy using MTX + SSZ + prednisone and (d) initial combination therapy using MTX + infliximab (INF). After 1 year of treating patients in the groups c and d, the results showed better functional improvement and less radiographic damage when compared with the patients in groups a and b [26]. After 2 years, 38–48% of patients in all four groups were in remission [27].

The Computer Assisted Management for Early Rheumatoid Arthritis (CAMERA) study was a randomised prospective multicenter trial. The goal of this study was to compare intensive versus conventional treatment, both strategies aiming for remission. After 2 years, more patients in the intensive group (50%) were in remission when compared to the routine treatment group (39%) [28]. In another study, the CIclosporine, MEthotrexate, STeroid in Rheumatoid Arthritis (CIMESTRA) study, remission rates were 59% and 54% for DAS28 remission and 41% and 35% for ACR remission after 2 years in the combination csDMARDs and monotherapy arms respectively [29]. The Treatment of Early Aggressive RA (TEAR) study using as initial treatment a triple combination csDMARDs therapy (MTX + HCQ + SSZ) was comparable with a step-up triple strategy. After 1 year, remission and structural damage progression were found to be similar in both groups [30]. In the second TEAR study by Moreland et al. [31], no clinical differences were detected after 1 year between the initial triple combination csDMARDs therapy (MTX + HCQ + SSZ) or step-up combination triple therapy versus MTX + Etanercept (ETN) [31]. The benefits of triple therapy were associated with the improvement of the lipid profile in RA patients. Indeed, the use of triple therapy (TEAR study) during those 2 years of follow-up was associated with higher levels of high-density lipoprotein (HDL) and lower LDL cholesterol levels, as well as improvement of the total cholesterol/HDL ratio. In the GUErir la Poly Arthrite Rhumatoide Debutante (GUEPARD) study, initial treatment with MTX plus adalimumab (ADA) was compared with initial MTX monotherapy and addition of ADA 3 months later if the DAS28 was > 3.2. After 1 year, the proportion of patients with LDA (65%) was similar in both groups, and there were no differences in structural damage progression [32]. In another study by O'Dell et al. regarding the clinical benefit of triple therapy with csDMARDs (MTX + HCQ + SSZ) was not inferior to ETN plus MTX in patients with RA who had active disease despite MTX therapy [33]. Van Vollenhoven et al. aimed to compare the addition of SSZ and HCQ versus the addition of INF to MTX in patients with early RA. After 1 year, patients with the addition of INF to MTX monotherapy were clinically superior to the addition of csDMARDs [34]. However, after 2 years, no differences have been observed between the two groups in terms of clinical and quality of life findings [35]. In a recent article by Verhoeven et al., a T2T and tight control strategy in early RA patients using tocilizumab (TCZ) or TCZ + MTX versus MTX + prednisone, showed similar clinical results as an initial treatment option [36]. Similar results have been reported by Schipper et al., and a meta-analysis concluded that tight control in RA patients resulted in significant better clinical outcome than the usual care

Table 1 Summary of results of T2T approach and tight control monitor disease activity in rheumatoid arthritis patients

Author, year (study name)	Drug strategy	Main results
Early RA		
Boers M, 1997 (COBRA) [11]	MTX + SSZ + prednisone (high doses) vs. SSZ	Combination therapy superior to SSZ to control disease activity
Landewe RB, 2002 (COBRA) [12]	MTX + SSZ + prednisone vs. SSZ	Combination therapy superior to SSZ inhibiting structural damage
Van Tyul LH, 2010 (COBRA) [13]	MTX + SSZ + prednisone vs. SSZ	Combination therapy normalised mortality rates as compared to SSZ monotherapy
Poppellaars PB, 2019 (COBRA) [14]	MTX + SSZ + prednisone vs. SSZ	Combination therapy had similar mortality rates to general population compared to SSZ monotherapy
Hetland ML, 2008 (CIMESTRA) [29]	Combination of csDMARDs vs. monotherapy of csDMARDs	Remission rates were higher in the combination group
Tight control		
Mottonen T, 1999 (FIN-RACo) [17]	MTX + SSZ + HCQ + prednisone vs. SSZ + prednisone	Patients in combination therapy were in remission after 2 years, as compare to monotherapy
Rantalaiho V, 2009 (FIN-RACo) [18]	MTX + SSZ + HCQ + prednisone vs. SSZ + prednisone	Sustained remission and reduced radiographic progression in the combination group, as compare to monotherapy
Rantalaihov, 2010 (FIN-RACo) [19]	MTX + SSZ + HCQ + prednisone vs. SSZ + prednisone	Combination therapy resulted in higher rates of remission even in the long term when compared to monotherapy
Grigor C, 2004 (TICORA) [25]	Tight control with csDMARDs vs. routine treatment	Tight control therapy showed remission rate of 65% as compare to usual care
Goekoop-Ruiterman YP, 2005 (BeSt) [26], 2007 [27]	a. Sequential monotherapy b. Step-up combination therapy c. Initial combination + prednisone d. Initial combination + INF	Groups c and d showed better functional improvement and less radiographic damage After 2 years, 38–48% of patients in all four groups were in remission
Verstappen SM, 2007 (CAMERA) [28]	Intensive vs. conventional treatment	More patients in the intensive group were in remission
Verhoeven, 2019 (U-Act-Early and CAMERA-II) [36]	TCZ or TCZ + MTX vs. MTX + prednisone	TCZ alone or in combination with MTX versus MTX + prednisone showed similar clinical results as initial treatment options
Triple therapy		
Saunders SA, 2008 (TEAR) [30]	MTX + HCQ + SSZ vs. step-up combination therapy	No differences between groups regarding remission and structural damage
Moreland LW, 2012 (TEAR) [31]	MTX + HCQ + SSZ or step-up combination therapy vs. MTX + ADA	No differences between groups concerning remission
Van Vollenhoven RF, 2009 (Swefot) [34]	MTX + HCQ + SSZ vs. MTX + INF	MTX + INF was superior the first years regarding clinical improvement
Van Vollenhoven RF, 2012 (Swefot) [35]	MTX + HCQ + SSZ vs. MTX + INF	After 2 years, no differences were observed between groups
O'Dell JR, 2013 [33]	MTX + HCQ + SSZ vs. MTX + ETN	Triple therapy was non-inferior to MTX + ETN

T2T, treat-to-target; *MTX*, methotrexate; *SSZ*, sulphasalazine; *HCQ*, hydroxychloroquine; *csDMARDs*, conventional synthetic disease-modifying antirheumatic drugs; *INF*, infliximab; *ADA*, adalimumab; *ETN*, etanercept, *TCZ*, tocilizumab; *APR*, acute phase reactant; *CDAI*, clinical disease activity index

[37]. A summary of the above studies including their results are shown in Table 1. In addition, the treatment strategies are presented in three different categories: (a) early RA, tight control and triple therapy studies.

The importance of early intervention and early disease control has been shown in many clinical trials. The Canadian Early Arthritis Cohort (CATCH) study was one of them, in which a delayed initiation of DMARDs reduced the probability of sustained remission [38]. In a multicenter observational study from Australia aiming for remission, disease activity improved over a 5-year period [39]. Kaltsonoudis et al. in a long-term observational study following the T2T approach and tight control strategy were able to treat and achieve LDA in the majority of patients [5]. Finally, Sokka et al. reported that a similar clinical response can be reached either by using bDMARDs or csDMARDs with the latter being less expensive. This last point may be recognised in future recommendations and guidelines for the management of RA [40]. However, the combination of csDMARDs and tight control strategies have not received wide popularity and acceptance in clinical practice. This may be due to the fact that not all rheumatologists follow the ACR/EULAR recommendations for

RA management and because the training and education in rheumatology differs among different countries. In addition, shared decision-making is an imperative to minimise the fear of overtreatment and adverse events [4].

Conclusions

In the past, the management of RA was a difficult task, and remission or LDA were a strange phenomenon due to the limited therapeutic choices in a rheumatologist's armamentarium. Today, the therapeutic armamentarium for RA has many choices with the old but also newer drugs, and remission makes its way to rheumatology. To this end, we would like to give emphasis to the fact that treatment decisions and strategies appear to be more important than just the drugs. Thus, T2T approach and tight control aiming for remission or LDA is a promising option to treat early RA patients. This strategy is less expensive in comparison to newer drugs and may be recognised in the future recommendations for the management of RA.

Compliance with ethical standards

Disclosures None.

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