



SHORT REVIEW

Clinical Course and Sustained Remission in Rheumatoid Arthritis

Mariana Lagrutta*, Roberto Leandro Parodi and Alcides Alejandro Greca

Systemic Autoimmune Disease Section, Internal Medicine Department, Hospital Provincial del Centenario, Universidad Nacional de Rosario, Argentina



*Corresponding author: Mariana Lagrutta, Systemic Autoimmune Disease Section, Internal Medicine Department, Hospital Provincial del Centenario, Universidad Nacional de Rosario, Rosario, Santa Fe, Argentina, E-mail: marianalagrutta@gmail.com

Abstract

Rheumatoid arthritis (RA) is an inflammatory, multisystemic autoimmune disease. It has been described as an often progressive chronic disease, characterized by severe functional decline, radiographic progression, frequent work disability and premature mortality. Efforts have been made to identify among patients with peripheral inflammatory arthritis which patients will have a benign course, with spontaneous resolution, and which will develop a chronic progressive inflammatory disabling disease if untreated. In recent years a remarkable improvement in RA patient outcome is observed. The two major approach changes that explain the better course of RA are the early diagnosis with subsequent prompt treatment initiation, and the treat to target strategy. The windows of opportunity theory sustains that in early stage of the disease autoimmunity may be reversed, and with prompt and intensive treatment even an antirheumatic drugs-free remission could be possible. Early and sustained remission became a feasible target leading to a much benign course of disease, in term of articular and systemic complication, quality of live, working disability and survival.

represents different diseases from the very beginning [4]. Moreover, it has been postulated that we should reconsider whether RA should be thought of as a syndrome with multiple etiologic events [5]. Nevertheless, different cohort studies show a better outcome in recent years in RA patient [6-8]. Evidence sustains that the disease prospects of patients newly diagnosed with RA today are much better than they were decades ago, and that this seems to be the result of several changes in treatment strategies [9-11]. Therefore we may assume that at least part of the clinical course of the disease can be modified by appropriate clinical management.

From Undifferentiated Peripheral Inflammatory Arthritis to Established RA

Recent onset arthritis is a common complaint both in primary care settings and in rheumatologic consultations. Undifferentiated peripheral inflammatory arthritis (UPIA) diagnosis is based on the failure to satisfy classification criteria for other well-recognized rheumatic conditions such as rheumatoid arthritis, psoriatic arthritis, gout, systemic lupus erythematosus, osteoarthritis, or other infectious, metabolic, traumatic or malignant etiologies [4,12]. Its estimated prevalence is between 30% and 50% of patients presenting to the rheumatologist [13]. In some of these patients, the disease evolves into other rheumatic conditions, while in many cases disease regresses [13]. UPIA should be constantly rethought, as patients may develop a disease that can be labelled with a specific diagnosis at any time [12]. Remission rate in UPIA range from 13% [13] to 57.9%, [14] while evolution to RA according to 1987 American College of Rheumatology (ACR) classification criteria [15] range around 14% [13,14]. Nevertheless persistent disease

Introduction

Rheumatoid arthritis (RA) is an inflammatory, multisystemic autoimmune disease. It affects 0.5% of the population and has been described as an often progressive chronic disease, characterized by severe functional decline, radiographic progression, frequent work disability and premature mortality [1,2]. However, it is also recognized that RA has a heterogeneous spectrum varying from mild, self-limited arthritis to severe permanently active and erosive polyarthritis leading to progressive joint damage, functional disability [3] and extra-articular manifestations [4]. It remains unanswered if the wide spectrum of clinical phenotypes is determined by a different set of risk factors, or if the subsequent course



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over 12 month and requirement of disease-modifying antirheumatic drugs (DMARDs) are described in up to 30% of UPIA patients [13].

Efforts have been made to try to predict which patients will have a benign course, with spontaneous resolution, and which will develop a chronic progressive inflammatory disabling disease. The identified predictors of persistent inflammatory arthritis includes: Disease duration of at least 6 weeks, duration of morning stiffness more than 30 minutes, functional impairment (by Health Assessment questionnaire (HAQ) score) in the first 3 month, failure to respond 2 weeks after local treatment with intra-articular corticosteroids, involvement of small joints and/or knees, presence of Rheumatoid factor (RF), presence and level of Anti-citrullinated protein/peptide antibodies (ACPA), functional status (by HAQ score), arthritis of at least 3 joints, proximal interphalangeal involvement, metatarsophalangeal joint involvement, and radiological erosion at the hands and feet [12]. Predictors of an eventual diagnosis of RA were the following: Advanced age, female gender, greater morning stiffness [12]. Other variables associated with progression to RA were: Higher number of tender and swollen joints, involvement of small joints of hands and feet, involvement of both the upper and lower extremities and symmetrical involvement. Similar features were associated with disease persistence and development of erosion, while self-reported functional disability by HAQ score and presence of extra-articular features, advanced age, female gender and longer symptoms duration were predictive of future disability [12]. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) showed some diagnostic value for the development of RA. Radiographic erosions, bone edema, synovitis and erosion pattern on resonance images also increased the probability of developing RA from UPIA [12].

Regarding genetic test, shared epitope (SE) showed poor diagnostic utility for RA, and was weakly associated with poor prognosis [12].

Cigarette smoking is a risk factor for the development of RA. It is associated with RF production, both in RA patients and the general population [4], and with induction of ACPA in HLA susceptible individuals. Smokers are more likely to develop erosions and extra-articular manifestations of RA [4]. Lung inflammation through smoking and changes in bacterial microbiote, as well as paradontopathies has also been identified as important inducers of autoimmunity [16].

Windows of Opportunity

Symptoms duration took on particular importance in disease course. Quinn, et al. [13] found in a large cohort of patients with undifferentiated arthritis of the hands followed over 12 months that early resolution of synovitis was associated with an excellent prognosis, suggesting that clinical decisions regarding a patient's further

management may be confidently made at 12 weeks. These findings are in line with those of Green [17], and suggest that very early inflammatory disease may differ immunologically from disease of longer duration, so that intervention at this stage, prior to the development of persistence, may offer a unique opportunity for a qualitative improvement in outcome [13]. Moreover, some authors have the hypothesis that autoimmunity could even be reversed in very early phase in some patients [18]. In the timeline of disease evolution, the appearance of autoantibodies and increased levels of proinflammatory cytokines have been described years before the development of AR [16]. In this pre-disease phase, individuals with ACPA, RF and SE positivity have a significant risk of RA, especially if they have arthralgia. This phase can be transformed into definitive RA associated with the acceleration of autoimmunity, further loss of tolerance and clinical symptoms [18]. In this early stage, the disease aggressive therapy leads to disproportionate benefits and patients have a good chance of remission [10,16,18,19]. In accordance with this window of opportunity theory, the potential reversibility of autoimmunity decrease over time in RA and this alters the potential efficacy of therapies [18].

Importance of Prompt Diagnosis and Early Intensive Treatment

Data from multiple observational cohorts and clinical trials indicate that treatment initiation in the first 12 weeks since disease onset is particularly effective in controlling disease activity and results in better mid-term and long term outcomes [11]. As mentioned above, the time to intervention within a limited time frame is associated with a particularly effective response to therapy, resulting in long term sustained outcomes [11].

In spite of these evidence, a study on UPIA [13] showed a delay on treatment of patients with persistent synovitis that didn't fulfilled the 1987 ACR classification criteria for RA, reflecting the reluctance to prescribe DMARDs in these patients, and the consequent continued prognostic and diagnostic uncertainty. Given that several of the 1987 ACR criteria [15], as radiological erosions and rheumatoid nodules are features of chronic or severe disease that may not appear until months or years after disease onset [4], new classification system that take account of features at earlier stages of disease were needed. The ACR and the European League Against Rheumatism (EULAR) developed new criteria focused on identifying factors that best discriminated patients who were at high risk for persistent and/or erosive disease among patients newly presenting with undifferentiated inflammatory synovitis [20], and strongly recommend treatment initiations as soon as RA diagnosis is made.

Some authors argue that the increased sensitivity of these criteria comes at the price of loss of specificity and carries the risk of overtreatment of patients whose dis-

ease would eventually resolve without DMARDs. However this risk has been demonstrated to be very low: 8% with 2010 ACR/EULAR criteria for RA compared with 2% with 1987 criteria. Later validation of these criteria confirmed their accuracy to select patients with worse clinical outcome and more radiographic progression, therefore needing aggressive treatment [11]. Careful and complete evaluation to rule out differential diagnosis of UPIA are essential to accurate classification and management [12]. It is essential to always keep in mind the 2010 criteria have been developed for classification purpose, and are an useful tool to reduce diagnosis uncertainty, particularly in early disease states. However RA diagnosis should be made in an individual bases, and medical judgment applied to a particular patient is the best instrument to achieve a faithful diagnosis.

The Treat to Target (T2T) and Tight Control Strategy

Growing evidence from randomized control trials and cohort studies supports that the T2T and tight control strategy is sometimes more important than the agent used to treat RA [6,11]. Whereas in the early 1990s DMARDs were commenced within two years after symptoms onset, DMARDs are now started as soon as diagnosis is made. Pincus observed in his cohort a better status for patients with RA in 2000 compared with 1985, over which an aggressive treatment strategy was implemented [6].

The task force recommendations for management of

RA in clinical practice provide guidance for treatment to target ('T2T') [21] that establishes an even more tight control to be achieved, as low-disease activity or remission, and not only improvement, are targeted. EULAR and ACR recent guidelines also follow this T2T strategy [22,23], and recommend a strict clinical monitoring, every 1 to 3 months [22], and adjusting therapy according to disease activity.

Remission in RA

As mentioned above, remission (or at least low disease activity) is the mayor aim of new treatment strategies. The reported remission rate varies depending on the nature of the study population, the definition of remission used and the time of assessment [24,25]. Remission definitions are described on Table 1. A rate around 10 to 30% was found in latter studies for patients classified as having RA according to the 1987 ACR criteria [4]. With the currently available synthetic and biological DMARDs, and a tight control strategy, remission is achievable in an increasing number of patients, around 20 to 40% [18]. It has been hypothesized that the major reason for persistent disease activity despite biologic therapy is the inappropriately late timing of therapy with biologic agents [19]. Some evidence show that patients treated at an earlier phase of disease can achieve a clinical remission rate of 70% and a response rate of above 95% [19].

The importance of the timing to achieve remission has also a fundamental prognostic role. In early RA,

Table 1: Criteria for remission, for rheumatoid arthritis ordered by Stringency (FDA criteria most difficult to fulfill) [24,25].

Score	Measurements	Remission definition
Disease Activity Score 28: DAS 28	28 tender joint count 28 swollen joint count ESR Patient's global assessment	< 2.6
Disease Activity Score: DAS or DAS 44	Ritchie articular index of tender joint 44 swollen joint count ESR Patient's global assessment	< 1.6
Clinical Disease Activity Index: CDAI	28 tender joint count 28 swollen joint count Patient Visual Global Assessment Physician Visual Global Assessment	< 2.8
and		
Simplified Disease Activity Index: SDAI	28 tender joint count 28 swollen joint count CRP Patient Visual Global Assessment Physician Visual Global Assessment	< 3.3
American College of Rheumatology criteria: ACR criteria	Morning stiffness < 15 minutes No joint pain by history No joint tenderness by examination No joint or tendon sheath swelling ESR < 30 mm/h (women) or < 20 mm/h (men) No fatigue	Minimum 5 of 6 over 2 month
US Food and Drug Administration FDA criteria	ACR criteria + radiographic arrest by Larsen or Sharp	ACR criteria + radiographic arrest for 6 month after medication discontinued

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

evidence demonstrated that earlier time to remission predicts sustained clinical remission, and it has been postulated that rapid induction of remission is essential to improve health-related quality of life and maintain workability [11]. Early treatment resulting in tight inflammation control and remission is strictly associated with improvement in cardiovascular risk and reduction of cardiovascular morbidity. Early and sustained remission is also associated with improved survival [11].

On the other hand, lifelong treatment with biological DMARDs is very expensive and entails potential long-term side effects [18]. According to EULAR [22] and ACR [23] recommendations, if a patient is in remission, biological DMARDs might be tapered. ACR guidelines clarify that tapering denotes scaling back therapy (reducing dose or dosing frequency), not discontinuing it, and if done, must be conducted slowly and carefully [23] (for withdraw of all DMARDs see below).

DMARDs-Free Remission in RA

The prevalence of medication-free remission seems to be around 3.6 to 22% [18]. Data from Ajeganova, et al. [10] revealed an increase in chance for DMARDs-free remission when patients were treated according to early and more intensive strategies in standard clinical practice. The most important findings were that when DMARDs-free sustained remission was achieved the functional ability measured by HAQ score was normalized. Also important, RA-related symptoms as pain and fatigue had resolved (visual analogue scale (VAS) were lower than reference range). They concluded that DMARDs-free sustained remission is a disease outcome reflecting health state close to expected in the general population with regards to functioning and several RA-related symptoms, and is increasingly achievable in recent years of early and intensified antirheumatic therapy [10].

These results are very optimistic, however, some caution should be made. In previous studies, in a large proportion of patients with established RA in remission, the withdraw of conventional DMARDs was followed by flares in about 70% of patients, twice as frequently as maintaining therapy irrespective of regimen [22,25]. In Tiippana-Kinnunen study [26] of early RA, 45% of patients who met the modified ACR criteria of remission had disease flares, and had to be restarted on DMARDs. The mean DMARDs-free period was 50 month overall, ranging from 3 to 137 months, showing that flares can occur at any point. In the 4-years follow-up of the BeSt study [27], the mean duration of drug-free remission was 9 to 11 months. Klarenbeek [28] also founded a mean remission time of 23 months, ranging from 15 to 25 months.

According to the windows of opportunity theory, a very early intensive treatment at the initial phase of the disease could have a more reversible state [18], and

could lead to the potential reverse of the autoimmune process. More studies are needed to identify those patients who have a realistic chance to taper and withdraw medications [18].

The 2015 ACR guidelines for treatment of RA [23] recommends that if the patient's disease is in remission, do not discontinue all RA therapies. In the same way, EULAR [22] guidelines pointed out that once sustained remission is achieved, conventional DMARDs reduction rather than cessation should be considered. On the other hand, drug-free remission may be an option in patients in whom therapy was initiated very early and who therefore also had achieved remission early in their disease course [22]. Close follow up is need in such cases, and patients must understand that disease can flare in any moment.

Systemic Involvement

High disease activity and extensive disability during the first 2 years after diagnosis have been shown to predict subsequent development of severe extra-articular manifestations. Smoking and high RF values are also predictive of this severe systemic involvement [29].

Cardiovascular complications

Studies have reported a 1.5 to 2-fold increase in risk of acute myocardial infarction, cerebrovascular disease or cardiovascular mortality in people with RA [30]. There is growing evidence that suggests that effective antirheumatic treatment reduces the risk of cardiovascular disease in rheumatoid arthritis [31]. As mentioned above, inflammation control and remission is strictly associated with improvement in cardiovascular risk and reduction of cardiovascular morbidity. In spite of the potential side effects of DMARDs, the sustained use of appropriate antirheumatic therapies, not only improves rheumatic disease itself, but also the cardiovascular complications. Inversely, the risk of myocardial infarction is increased in nonsteroidal anti-inflammatory drug (NSAID) and cyclooxygenase 2 inhibitor users [31]. A recent metaanalysis confirmed an increased risk of major vascular events for these drugs, except for naproxen [32].

Other complications

Infectious complications are a concern in all RA patients, in particular those on biological DMARDs. A vaccination protocol, rule out occult infections and explanation of warning signs are critical. Prevention of osteoporosis and contraception in women of child-bearing potential must also be considered.

Achieving target inflammatory control requires a very close monitoring and regular assessment of disease activity. Additional tasks are the evaluation of extra-articular manifestations, cardiovascular and gastrointestinal risk factors and complications, infection detection and managing, and monitoring DMARDs adverse

events. Patient education to follow strict recommendations are also needed. It has been reported that RA in association with extra-articular disease and co-morbidity accounted for 22% of RA-related work disability. Identifying risk factors and managing these conditions early is an important part of RA patient management [33]. A multidisciplinary approach may facilitate these tasks and probably allows a better outcome.

Conclusions

The two major approach changes that explain the better course of RA are the early diagnosis with subsequent prompt treatment initiation, and the treat to target strategy. Remission is now a feasible target that should permanently be aimed. A multidisciplinary approach is very useful to take account of systemic manifestations and possible complications of the disease and its treatment. Education is always an important tool to reach better compliance and therefore better outcomes. Primary care practitioners, patients and general population should be aware of the risk of the inflammatory joint complaints, and the importance of its intensive treatment in order to promote early referral and a close follow-up.

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