

When the first visit to the rheumatologist is established rheumatoid arthritis

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Abstract:

The outlook for people living with rheumatoid arthritis has improved tremendously in a generation. Major contributions to this include recognition of the importance of early treatment initiation, improved understanding of the pathobiology, identification of therapeutic targets and their subsequent validation in clinic trials; and the realisation of the importance of “tight control” of inflammatory responses. Despite these advances, many patients meeting classification criteria present for the first time to a rheumatologist with longstanding symptoms. There is no definition as to when rheumatoid arthritis becomes “established”. But there is evidence that a “window of opportunity” exists over about 12-16 weeks symptom duration during which treatment intervention gives rise to the most optimal outcomes. This review addresses issues regarding management of patients presenting outside the window of opportunity in terms of heterogeneity of presentation, assessment, therapeutic goals and treatment options as well as the importance of a multidisciplinary approach to holistic care.

Key words:

Rheumatoid arthritis

Established disease

Disease-modifying anti-rheumatic drugs

Targeted therapies

Clinical assessment

Management

Introduction

Rheumatoid arthritis (RA) is best thought of as an inflammatory syndrome with autoimmune features with its predominant expression in synovial joints. It is the most common form of

inflammatory polyarthritis. There are no laboratory tests that are pathognomonic for RA, but the presence of anti-cyclic citrullinated protein antibody (ACPA) and/or IgM rheumatoid factor are relatively specific for this condition. However, neither of these tests are sufficiently specific to establish the classification of RA, and prognosis varies widely within seropositive and seronegative patient populations, respectively. These autoantibodies can be detected in the blood in about three quarters of patients. Recognising that best outcomes are achievable when treatment intervention is as early as feasible in the evolution of the illness, updated classification criteria were published in 2010 by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) with a view to encouraging timely introduction of treatment [1].

Such an approach may prevent joint damage and deformity, preserve function and prevent the development of systemic complications of disease [2-4].

The clinical presentation of RA is heterogeneous, with a wide spectrum of age of onset, degree of joint involvement, and severity. The variability of the presentation and clinical course in the earliest stages of the illness is such that diagnosis, or classification, can be difficult. Similarly, the disease course can be highly variable. Once established and, if persistently active, RA becomes characterized by a deforming symmetrical polyarthritis of varying extent and severity. It may be associated with synovitis of joint and tendon sheaths, articular cartilage loss and erosion of juxta-articular bone, and, in most patients, the presence of IgM rheumatoid factor and/or ACPA in the blood. By two years after symptom onset, joint erosions are present in 50-70% of rheumatoid arthritis patients [5]. In the early stages of RA there is a high correlation between disability and inflammation and little clear-cut relationship to radiographic damage [6]. However, as the disease becomes more established and time passes, structural damage becomes a major determinant of functional disability.

In a proportion of patients systemic and extra-articular features may be observed during the disease course (and rarely prior to joint disease). Such features include anaemia, osteoporosis, weight loss, vasculitis, serositis, nodules in subcutaneous, pulmonary, and sclera tissues, mononeuritis multiplex, and pulmonary interstitial inflammation as well as exocrine, salivary, and lachrymal gland involvement. Other comorbidities commonly observed in established RA include cardiovascular disease, infection, depression, and certain malignancies. As appreciation of the gravity of the social and economic burden imposed by RA has grown, so has the recognition that more favourable clinical outcomes are achieved when synovitis is optimally suppressed.

What is meant by “established” RA?

There is no consensus as to the definition of “established” as opposed to “early” RA. Any such theoretical distinction has become more challenging with the recognition that autoantibodies such as RF and ACPA may be present many years prior to the appearance of symptoms of RA [7]. However, for pragmatic purposes and feasibility of recruitment, many clinical trials have defined “early” as having less than 2 years disease duration (from the time that classification criteria have been documented as being fulfilled). Even then, such populations may include subjects with much longer symptom duration unless recruitment criteria distinguish symptom duration from duration since classification criteria were met. The term “very early” RA has been used to refer to patients with less than 3 months of symptom duration [8]. The revised 1987 ACR classification criteria for RA were based on a hospital population of patients with established, active disease [9]. These criteria combine a constellation of clinical, serological, and radiological features, and for many decades were widely accepted for epidemiological and clinical studies. By emphasizing key features of the syndrome, the criteria helped to differentiate RA from other forms of inflammatory arthritis, with a sensitivity and specificity of about 90% for active disease. However, these requirements have a much poorer sensitivity for the classification of RA in the early stages of presentation, where the sensitivity of the classification criteria ranges from 40% to 60%, and the specificity is no better than 80-90% [10-15].

A major emphasis in rheumatology over recent years has been on the early diagnosis and treatment of RA in order to best realise opportunities to achieve and sustain the ideal goal of remission. The ACR-EULAR 2010 classification criteria for RA were formulated with this aim in mind. The importance of this approach has been confirmed by both formal clinical trials and monocentric clinical cohort studies which strongly support the concept that a window of opportunity exists, within the first 12–16 weeks from symptom onset, in which the best outcomes in RA are most likely to be realised [16-20]. In order to achieve such early intervention, public health campaigns are desirable in order to alert people with newly presenting symptoms to seek specialist help. And furthermore, in circumstances where referral to the rheumatologist is via a family physician, it is important that the family practitioner is aware of the importance of early referral and that pathways are in place to facilitate this. But even with best intention, there will be many instances where people with arthritis will first be reviewed by a specialist when they are in the established phase of disease. Or they may be seen with active and established disease having responded inadequately to initial therapy. The focus of this article concerns management of these people presenting in the established phase of RA.

A delayed rheumatological referral (≥ 12 weeks) has been associated with a long-term impact, with a hazard ratio of 1.87 for failure to achieve disease modifying anti-rheumatic drugs (DMARD)-free remission and a 1.3-fold higher rate of joint destruction over 6 years. Unfortunately, despite robust evidence supporting the relevance of a window of opportunity, only 31% of patients with RA were assessed within 12 weeks of symptom onset in a real-life setting of 1674 patients with early arthritis [18]. A meta-analysis of 18 randomised controlled trials reported that prolonged symptom duration before DMARD initiation is independently associated with radiographic progression and a lower probability of DMARD-free sustained remission [21]. Earlier time to remission is the strongest predictor of a sustainable response over a 20-year period regardless of the type of treatment [22]. Disease duration is among the most relevant factors affecting the likelihood of patients' response to treatment [23,24], even when biologic DMARDs (bDMARDs) are prescribed [25,22]. Patients with early arthritis referred to a specialist within 3 months show better outcomes in terms of drug-free remission, radiographic damage and reduced need for orthopaedic surgery than those with late referral [26]. Nonetheless, contemporary therapeutic strategy is similar in both early and established RA by means of a treat-to-target approach with an ideal goal of remission and prevention of joint destruction. This will be discussed more fully in the context of established RA in subsequent sections.

General principles underlying the management of established RA

A multi-disciplinary approach to the holistic management of RA

It is important to recognize that pharmacological intervention represents only one aspect of the management plan for RA at any given stage of disease, irrespective of its severity. Other important aspects of the total management plan include patient education and, where necessary, psychological and employment counselling. A realistic evaluation of the most appropriate level of rest and exercise and coping with activities of daily living can help to support the optimum quality of life and functioning achievable by a given individual living with RA. In this respect, appropriate access to splints, aids, and adaptations can help preserve function and maintain independence and mobility. Counselling and information about access to social and financial benefits is also of great importance. Appropriate comfortable footwear and proper care of the feet, particularly in those patients with established deformities, can help maintain mobility and comfort. Surgical treatment may play an essential role in relieving intractable pain and may help restore physical functioning and mobility lost as a result of mechanical damage to joints and associated structures. Surgery may also be invaluable

in the treatment of secondary complications of joint disease, such as peripheral nerve entrapment at the wrist or elbow, and cervical cord compression in relation to instability of the cervical spine.

The success of pharmacological intervention requires that the patient, where possible, is involved in the reasoning behind recommendation of a given therapeutic approach and provides informed consent to the treatment regime [27]. Family members and carers may also wish to be involved in this process and to have a thorough understanding of the potential benefits and risks of treatment as well as appropriate drug monitoring and other means of mitigating the risk of any toxicity. Because RA is a chronic disease, most patients will establish long term relationships with their health care providers. Multi-disciplinary teamwork is key to the success of a holistic approach to patient care involving several allied health care professionals, including specialist nurses, physiotherapists, occupational therapists, podiatrists, social workers, pharmacists, and surgeons. Furthermore, it is essential to establish good co-ordination of patient care between physicians in primary and secondary care settings.

Clinical assessment of people presenting with established RA

On the first visit to the rheumatologist, a full medical history and thorough clinical examination should be undertaken and the findings recorded. Evaluation for comorbidity should be a crucial part of the medical assessment.

Symptoms related to RA are assessed by taking a descriptive history and by attempting to quantify their severity. Similarly, signs of rheumatoid arthritis are documented following a careful examination. Synovial thickening is detected on palpation as a spongy or boggy feel, and tenderness is elicited by squeezing an affected joint. It is always best to do this gently in the first instance! Other classical signs of inflammation such as erythema or raised temperature overlying the affected joint are not as prominent or readily quantifiable on clinical examination alone. Joint effusions can be demonstrated by fluctuation. As RA progresses, deformities may advance and subluxed surfaces of bones may falsely give the impression of bony swelling. This is particularly evident at the heads of the metacarpals in the hands, the ulnar styloid, and the distal radius at the wrist.

A careful evaluation of RA disease activity by means of one of several available and validated composite scores [28] will help inform the most appropriate pharmacological management and the subsequent titration of pharmacotherapeutic intervention according to assessment of clinical response by means of the same composite score at regular follow up visits. The primary aim of such a tight control approach while taking care to observe appropriate safety precautions is to limit or prevent structural damage and preserve functional status. Although treating-to-target is most

effectively applied at the earliest stages of RA it has an important place in the management of established RA when there is an active inflammatory component. This has been abundantly confirmed in many clinical studies adopting a “treat-to-target” paradigm [22,27].

It is advisable to become familiar with one of the available composite scores and to use this routinely for the assessment and follow up of patients presenting with established RA. These scores are largely derived from components of the ACR core set of seven measures [29]. Three of these measures should be assessed by the rheumatologist comprising a swollen joint count, tender joint count and physician assessment of global status. Three are assessed by patient self-report comprising physical function, pain and global health status. There is also one acute phase reactant comprising either ESR or CRP. The disease activity score (DAS) is derived from a formula based on information concerning the number of swollen joints, the number of tender joints, the acute phase response with or without the patient’s own assessment of global health status based on a 100 mm visual analogue scale. Various formulae have been derived, depending on the numbers of joints assessed (either 44 (DAS44) or a more limited set of 28 (DAS28)) and whether ESR or CRP is used as the acute phase reactant. This composite score gives rise to a continuous measure of rheumatoid disease activity. For DAS28, a score of greater than 5.1 represents a high level of disease activity; a score of less than 5.1 and greater than 3.2, moderate disease activity; a score of 3.2 to 2.6, near remission; and a score of less than 2.6 represents remission. It should be noted that the DAS28 cut-off values calculated using CRP are lower than those using ESR as the acute phase reactant [30]. The DAS 28 is widely used for assessment of disease activity and therapeutic response and is calculated automatically when the variables involved are entered into a computer in the clinic. In order to simplify clinical assessment, the Simplified Disease Activity Index (SDAI) was developed [31]. An overall continuous measure of RA disease activity is derived by the addition of the following individual measures: 28–swollen joint count (28SJC), 28–tender joint count (28TJC), patient global assessment of disease activity (PtGA) on a 10-cm visual analogue scale (VAS), provider global assessment of disease activity (PrGA) on a 10-cm VAS, and C-reactive protein (CRP) level in mg/dl. The level of disease activity can be interpreted as remission ($SDAI \leq 3.3$), low ($3.3 < SDAI \leq 11$), moderate ($11 < SDAI \leq 26$), or high ($SDAI > 26$) [32]. The smallest detectable difference for the SDAI is 8.26 [33].

A potential disadvantage of both the DAS28 and SDAI is the requirement of a current CRP value which may not be immediately available in clinic. To overcome this limitation, the Clinical Disease Activity Index (CDAI) was formulated as the addition of the following physician- and patient-derived clinical measures: 28SJC, 28TJC, patient global assessment of disease activity (PtGA) on a 10-cm VAS, and PrGA on a 10-cm VAS [34]. The level of disease activity can be interpreted as remission (CDAI

≤2.8), low (2.8 < CDAI ≤ 10), moderate (10 < CDAI ≤ 22), or high (CDAI >22) [34]. The smallest detectable difference for the CDAI is 8.05 [33].

Assessment of patient symptoms

Once RA becomes established, only a minority of patients in real world practice both attain and maintain a robust remission [35,36]. Nonetheless, minimizing the inflammatory burden of RA remains an important goal which is best achieved using a goal-oriented approach with a consequent improvement in clinical signs and patient-reported outcomes (PROs) [37]. By assessment of PROs, the rheumatologist can consider individual patient perceptions of disease impact as well as disease activity measures. Patient-centred treatment should involve shared goals with respect to what matters most to individuals living with RA [38]. PROs can be used in established RA to complement disease activity as a treatment target and with a view to informing management decisions about appropriate interventions. There are many available PROs [39]. For use in clinical practice they need to be short and simple to understand and can usually be completed by a patient in clinic prior to seeing their rheumatology health care professional. Examples of widely used PRO measures include the PtGA and the pain VAS. Others which assess several symptom domains include the Routine Assessment of Patient Index Data-3 (RAPID-3) [40] and the Rheumatoid Arthritis Impact of Disease (RAID) instrument [41]. RAPID-3 includes three domains; pain (VAS), disease activity (PtGA VAS) and physical function (multidimensional [MD]-Health Assessment Questionnaire [HAQ]), each scored on a scale of 0–10. Total scores range from 0–30, with higher scores indicating greater pain and disease activity, and worse physical function [40]. RAID was developed as a EULAR initiative to combine the most important PROs into one measure [41]. It consists of seven domains covering pain, physical function, fatigue, sleep, physical and emotional well-being, and coping. Each domain is scored using a numeric rating scale, giving a total RAID score of 0–10, with higher scores indicating greater disease impact. A RAID score of <2 is considered to be a “Patient Acceptable Symptom State” [42].

Assessment of structural damage to joints

Persistent disease activity over the course of disease often results in progression of structural damage to joints, although the rate and extent of damage in established RA is highly variable. Evaluation of the extent of structural damage to joints in established RA at first presentation provides a valuable baseline assessment that may contribute to the choice of therapy and can be compared with subsequent assessments to determine the influence of therapy in limiting damage progression. Imaging technologies are required to assess and quantify structural damage to joints. Conventional radiography is the most widely used imaging modality. There are also limitations, including the use of ionizing radiation and projectional superimposition that can obscure erosions

and mimic cartilage loss as an inevitable consequence of representing a three-dimensional structure in only two planes. Radiographs of the hands and feet are recommended in all patients at first presentation as well as baseline chest radiograph prior to potential commencement of methotrexate (MTX).

Formal quantification of structural damage requires experienced readers and the methods can be time-consuming. For this reason, such evaluation is usually restricted to clinical trials or studies. For routine clinical purposes, change in radiographs cannot usually be reliably determined in less than twelve months. Alternative imaging modalities including MRI and ultrasonographic technologies emphasize the inadequacy of conventional radiography for soft tissue assessment in RA.

The role of ultrasound assessment of established RA

Ultrasonography has emerged as a widely used tool for evaluation of soft tissue involvement in established RA and can supplement clinical examination in the detection of subclinical synovitis. Being non-invasive and without ionising radiation, it is readily acceptable to patients and can be helpful in the context of shared decision making by visibly demonstrating the presence or absence of inflammation to the patient. Grey scale ultrasonography (US) identifies synovial thickening without differentiating actively inflamed from fibrous tissue. Synovitis in the active phase of disease is metabolically active and vascular. Power Doppler ultrasound (PDUS) enables detection of low velocity blood flow such as that in inflamed small joints of the hands and wrists [43]. Vascular signal on PDUS has significant correlation to histologic findings of synovial vascularity and is a reliable method for assessing joint inflammation [44] with superior sensitivity to clinical examination [43,45]. However, it is important to take clinical context into account when interpreting ultrasonographic findings. For example, low grade vascular signal is commonplace in patients with concomitant osteoarthritis and not all patients meeting composite criteria for active disease have ultrasound evidence of power Doppler signal [46]. It has been argued that treating to a target of ultrasonographic imaging remission might afford tighter disease control and therefore better clinical and radiographic outcomes than treating to a remission target defined by composite clinical scores. However, two studies have now refuted this concept [47,48].

Assessment of function

Evaluation of patient function and disability by means of patient self-reported assessment (rather than physician assessment) has become standard in the context of randomized clinical trials. It is also useful to document this at first presentation of established RA. It is not necessary to repeat at every subsequent visit but can be informative as part of an annual review of progress. The most commonly used assessment tool for functional disability is the Stanford health assessment

questionnaire (HAQ) and its derivatives [49]. The HAQ and similar questionnaires primarily measure function and health-related quality of life. However, it should be noted that such questionnaires do not discriminate between the extent of functional impairment due to currently active disease (that is process-related and therefore potentially reversible) and the inevitable sequelae of long term, irreversible joint destruction.

Laboratory tests

There are many different circumstances in which a patient meeting classification criterion for RA who has been symptomatic for some time may first present to a rheumatologist. The diagnosis may have been established elsewhere previously in which case it is likely that autoantibody status will already have been assessed. But if presenting for the first time to a specialist, then blood tests to consider include rheumatoid factor and ACPA screening as well as anti-nuclear antibody screening. Other routine tests include full blood count and differential, blood biochemistry including liver function tests and acute phase markers. Other useful investigations to consider at baseline (if not available from a referring clinician) include fasting lipids and glucose. If a patient previously diagnosed and initiated on DMARDs presents for the first time to a rheumatologist with DMARD-refractory RA, as might occur, for example, after a house move, targeted therapies may be considered as a treatment option. In such a situation or if otherwise clinically indicated, additional blood tests would include hepatitis and mycobacterial screening tests.

Treatment goals

The goals of therapy in RA have been continually revised over the last one or two generations. There have been several reasons for this. In past generations the diagnosis tended to be made late and was not perceived as immediately life threatening. As such, treatment strategy was based on the premise of a generally favourable prognosis. However, careful studies of the natural history of RA clearly indicated that the majority of patients with a more aggressive disease course become clinically disabled within twenty years and for those with severe disease or extra-articular features, the mortality is equivalent to that of patients with three-vessel coronary artery disease or stage IV Hodgkin's lymphoma [50]. As a result, the notion that RA is a benign condition has been entirely discredited. Prior to the present millennium, the focus of treatment was on symptom amelioration. Subsequently, numerous clinical studies established that better outcomes can be achieved with optimal and early use of oral DMARDs, either singly or in combination, with a clear demonstration that significant improvement in efficacy need not be at the expense of unacceptably high toxicity or tolerability problems. The advent of targeted therapies heralded by the introduction of biologic agents directed against TNF further improved the expectation for magnitude of improvement in

symptoms and signs of disease. By means of treat-to-target strategies designed to intensively suppress synovitis, remission has become an achievable goal for a proportion of patients. The principle aims of a tight control approach as originally conceived were to limit or prevent the potentially devastating impact of structural damage in RA and preserve functional status. Although these aims remain an imperative of RA management, the problem of progressive structural damage to joints has become less marked in contemporary times than it was in past RA populations [51]. Many possible reasons for this include environmental changes (for example, changing smoking behaviour, better oral hygiene, fewer serious infections, and better overall nutritional status) in addition to the expansion of the therapeutic armamentarium and the drive towards earlier diagnosis and treatment of RA. Consequently, while prevention of deformity and functional loss remain key long-term treatment goals, as are prevention or limitation of co-morbidities and mortality, the nature of unmet need is shifting away from being predominated by inexorably progressive joint destruction. Many symptoms most troublesome to patients with established RA are subjective in nature and their true impact is known only to the patient themselves [38]. Examples include pain, fatigue and mental function, all of which can adversely affect social interactions, employment, sexual activity, and overall well-being [52].

In summary, the ideal goals of management of established RA include remission induction (to the extent achievable) with a view to control of symptoms and signs, prevention of structural damage with preservation and improvement of function, prevention and improvement of co-morbidity and reduction in RA-associated mortality. Closely aligned to these goals include the overarching aim of restoration and maintenance of a quality of life that permits the individual to pursue normal work, domestic, and social activity.

Comorbidities

It is estimated that the average patient with established RA has 1.6 comorbid conditions [53], and the number of conditions increases with age, disease duration and disease activity. The presence of comorbidities has been linked to reduced life expectancy, greater functional impairment and decreased quality of life [53,54]. A large international population based, cross-sectional study (COMORA) evaluated prevalence of comorbidities in patients with RA (n= 3920) from 17 countries around the world [55]. The most commonly reported comorbidities (past or current) were; depression 15%, asthma 7%, cardiovascular events (myocardial infarction, stroke) 6%, solid-organ malignancies, 5%, and chronic obstructive pulmonary disease 4%. They also reported wide intercountry variability for prevalence of these comorbidities, e.g. prevalence of depression was 2% in Morocco compared to 33% in the USA. Data from the British Society of Rheumatology Biologics register evaluated 7818 patients with established RA initiating biologic therapy [56]. They reported

58% of patients having at least one comorbidity and 25% having more than one, with cardiovascular, respiratory disease and depression being the most frequent comorbid conditions.

Comorbidities can negatively influence disease outcome, including the achievement of treat-to-target goals [57,35], as well as patient's self-management, utilisation of healthcare, and have a major impact on personal and health system related costs. In contemporary practice, the focus in the management of RA has increasingly emphasised 'treating RA to target' as the primary objective but with respect to established RA in particular, the role and impact of comorbidities on achieving these targets has received less attention both in the literature and often in the clinic. Current management guidelines for RA do not comprehensively address the complexity or any trade-off between efficacy and safety issues when treating patients with comorbidities [58].

When assessing established RA presenting for the first time, it is necessary to manage any existing comorbidities as well as formulating a strategy designed to prevent the arising of potential future comorbidities. Screening for comorbidities is important but a comprehensive and systematic approach can be time consuming and always not possible to carryout in a busy rheumatology clinic. However, clinical services can be organised to address this in the established RA population in, for example, dedicated annual review clinics or nurse-led screening programmes which have been shown to be effective in managing cardiovascular risk, vaccination uptake and osteoporosis [59]. Appropriate use of PROs can also be a valuable, efficient and cost-effective method for screening for comorbidities [60]. EULAR guidelines recommend influenza and pneumococcal vaccinations in all patients with autoimmune diseases [61]. Patients with established RA are at increased risk of developing osteoporosis, with studies reporting double the risk compared to the general population [62]. Glucocorticoid-induced osteoporosis is the most common cause of secondary osteoporosis [63], with risk of vertebral fractures increased up to two to five times, which is dose dependent [64]. EULAR has published guidelines for safe use of glucocorticoids [65-66] and recommendations for annual cardiovascular screening for patients with established RA [67]. However, evidence shows that management of these risk factors is far from ideal [68] with 30-50% patients with RA lacking optimal cardiovascular risk monitoring and management [55].

EULAR have recently published points to consider for reporting, screening and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice [69]. These recommendations emphasized three main principles. 1) Comorbidities such as cardiovascular diseases, malignancies, infections, osteoporosis, peptic ulcer and depression should be carefully assessed and managed in patients with chronic inflammatory rheumatic diseases. 2) All clinicians including health professionals such as nurses, treating general practitioners and rheumatologists and patients through self-administered questionnaires and self-management programmes play a key role

in the screening and detection of comorbidities. 3) Comorbidities should be subject to a systematic, standardised periodical review (e.g., at least every 5 years) for those with a chronic inflammatory rheumatic disease. The recommendations included a detailed practical form that can be used in daily clinical practice which focused on six selected comorbidities; cardiovascular disease, malignancies, infections, gastrointestinal diseases, osteoporosis and depression. Rheumatologists in France have aimed to implement these EULAR guidance points to collect and report comorbidities and to develop management recommendations for selected comorbidities for the treating rheumatologist to use in daily practice [70]. One of their aims was to provide rheumatologists a pragmatic guide with specific screening questions but also to inform which patient requires expert input from other specialities in a multi-morbid model of care and when referral should be made.

Pharmacotherapeutic management

The pharmacological armamentarium

Patients presenting with established RA typically require continued drug administration to control disease activity. By contrast, very early initiation of DMARD treatment for RA, before the onset of erosions, reduces the risk of joint damage and disability in comparison to DMARD initiation once RA becomes established [2,3,4]. In established RA, delayed treatment initiation and late achievement of remission (or failure to achieve remission) are major predictors of poor long term clinical, functional and radiographic outcomes. A delay in referral is one of the most important causes of late diagnosis and a corresponding delay in initiating effective treatment.

The heterogeneity of presentation of RA and subsequent course of disease into the established phase is such that pharmacological treatment will need to be tailored to the needs of the individual, considering their own preferences and personal goals pertinent to their stage in life. Abrogation of inflammation is considered the most important way to achieve optimal outcomes, particularly in the earlier stages of this chronic condition. It has long been known that many of the symptoms associated with active RA throughout the lifetime of a patient represent generic features of inflammation and it is for this reason that a treat-to-target strategy is strongly recommended. But it is also clear that certain symptoms have a multifactorial aetiology and may be the result of both inflammatory and/or non-inflammatory processes including the mechanical sequelae of longstanding disease. This may influence the choice of therapy in established RA while striving to fully address the inflammatory component of the presentation.

The few decades have witnessed unprecedented advances in our understanding of the pathophysiology of RA and this has been translated into a broad range of efficacious, so-called “targeted”, therapies directed against relevant cells and molecules contributing to disease

expression. These include parenterally administered bDMARDs and orally available targeted synthetic DMARDs (tsDMARDs). Other medications with a longer history that have disease-modifying potential include glucocorticoids as well as conventional synthetic DMARDs (csDMARDs), the most commonly prescribed being MTX, leflunomide, sulfasalazine, and hydroxychloroquine. Unlike DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs) improve certain features of inflammation, particularly symptoms of stiffness and pain, but have no capability to modify the rate of structural damage to joints in human disease, although they may do so in animal models.

There are four different classes of currently approved bDMARDs comprising tumour necrosis factor (TNF) inhibitors, antibodies directed against interleukin 6 receptor (IL6R), antibodies directed against the CD20 antigen expressed on a B cell subset and an inhibitor of the CD28-CD80/86 co-stimulatory signal necessary for T cell activation. The first generation of bDMARDs, referred to as bio-origins, were approved with finite patent life. Following patent expiry of the earliest bio-originator bDMARDs, biosimilars have emerged. A biosimilar is a biological medicinal product that is highly similar to an already authorized original biological medicinal product (reference medicinal product or bio-originator) in terms of quality, safety and efficacy, based on a comprehensive comparability exercise. Following their introduction to the clinic, high procurement costs of bio-originator bDMARDs have presented a challenge to access in many health care economies. In the case of the anti-TNF bDMARD class, bio-origins included three monoclonal antibodies (infliximab, adalimumab and golimumab), a TNF receptor fusion protein (etanercept) and a pegylated antibody-binding fragment (certolizumab). There are now several biosimilars of infliximab, etanercept and adalimumab which are introducing cost-competition and may potentially widen access to the anti-TNF bDMARD class. Similarly, in the case of rituximab, an anti-CD20, there are now approved biosimilars. As of the time of writing, there are two bio-originator anti-IL6R mAbs, tocilizumab and sarilumab, and one bio-originator directed against CD80 and 86, abatacept, a fusion protein composed of the Fc region of the human IgG1 fused to the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).

In contrast to bDMARDs, which are large molecular weight proteins that must be injected and are incapable of penetrating the lipid bilayer of cell membranes, tsDMARDs are low molecular weight, orally available, “small-molecules”. The only tsDMARDs currently available for the treatment of RA are inhibitors of janus kinase (JAK) enzymes, a family of four intracellular tyrosine kinases that function as “intracellular switches” in the signalling processes of the Type I/II family of cytokines and for certain growth factors after engagement with their receptors [71]. JAK inhibitors, or jakinibs, are multi-cytokine inhibitors that can cross the cell membrane to block activity of one or more cytoplasmic JAKs. There are currently two JAK inhibitors approved for treatment of active RA [72]

and others are in development. Tofacitinib selectively inhibits JAK1 and JAK3 and was the first JAK inhibitor to be approved, initially with twice daily dosing. A modified release formulation for once daily use has since been developed. Baricitinib selectively inhibits JAK1 and JAK2 and is dosed once daily. Both drugs have undergone extensive clinical trials and demonstrated rapid improvements in symptoms and signs when used in combination with concomitant MTX, other conventional disease modifying anti-rheumatic drugs (cDMARDs), or as monotherapy [72] with benefits reported as early as 2 weeks. Both agents inhibit structural damage progression. Remarkably, in MTX inadequate responders, the combination of MTX and baricitinib 4mg od demonstrated superiority for ACR20 responders and DAS28-CRP reduction over the standard of care biologic adalimumab used with background MTX [73].

Treatment recommendations

EULAR recommends treatment with csDMARDs including MTX upon initiation of treatment for RA [74]. Based on its efficacy, safety, large dose-titratable range, options for either an oral or parenteral route of administration, and cost-effectiveness, MTX holds a unique place in the management of RA [75]. MTX monotherapy is recommended as an initial pharmacological strategy but it can also be used as an “anchor drug” in combination with another csDMARD, any bDMARD or tsDMARD. MTX is currently the most commonly used first-line therapy for RA in the world [76]. Nonetheless, many patients with established RA do not achieve treatment targets with MTX monotherapy [77]. Short-term glucocorticoid use should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible [74].

First-line targeted therapy

If the treatment target is not achieved with the primary csDMARD, if there are poor prognostic factors present (such as high disease activity, rheumatoid factor positivity, presence of ACPA, or erosions) or if the patient has already failed to respond adequately to a combination of two or more csDMARDs, a bDMARD or tsDMARD should be considered. A targeted therapy would usually be added to background MTX (or other csDMARD) in the first instance. However, more than a third of patients are intolerant of MTX so approximately 30% of patients in clinical practice are treated with bDMARD eventually take this as a monotherapy [78]. All bDMARDs demonstrate better efficacy when combined with concomitant MTX as compared with use as monotherapy. This may be due to complementary mechanisms of action, pharmacokinetic interactions and reduction in immunogenicity of the administered bDMARD. Therefore, if a patient is intolerant of high dose MTX,

rather than substituting a bDMARD, it is worth considering reducing the MTX dose to a level tolerated and adding a bDMARD. In clinical studies in combination with the anti-TNF agent adalimumab, oral MTX at 10 mg weekly was reported to give similar clinical outcomes and bDMARD pharmacokinetic profiles as 20 mg weekly [79].

In general, based on indirect comparisons, approved bDMARDs have similar efficacy when used in combination with MTX [80]. In a direct comparison, the efficacy of abatacept and adalimumab were compared in MTX-refractory and bDMARD-naïve patients who continued background MTX [81]. The efficacy and kinetics of response of both bDMARDs was remarkably similar. At present there is a paucity of data supporting evidence-based prioritization of currently available bDMARDs of different mechanisms of action when used in combination with concomitant MTX. This situation highlights the need for a research agenda for identification of treatment stratifiers that enrich for the most favourable benefit:risk profiles and provide the most cost-effective care [80-82]. In the case of bDMARD monotherapy, in head-to-head studies inhibition of IL6R gives rise to superior efficacy outcomes than TNF blockade [83-84].

If disease activity in a patient with established RA is inadequately controlled by csDMARDs alone, the choice of subsequent therapy will depend on several factors, not least considerations of benefit versus potential risk and the view of the patient as to the acceptability of this. For example, in patients with a history of previous serious infections, the ACR conditionally recommends to use csDMARDs in combination over TNF inhibitors, or to use abatacept preferentially over TNF inhibition in these high risk patients, as supported by low level evidence from the ATTEST trial [85-87].

Given the broadly similar efficacy of different classes of targeted therapy, the choice of most appropriate bDMARD or tsDMARD for a patient after failure of initial csDMARD(s) will depend on many factors. There is compelling evidence supporting higher efficacy for rituximab in seropositive patients than in those who are seronegative [88]. In the case of patients unable to take concomitant csDMARDs, bDMARDs directed against IL6R or tsDMARDs have efficacy advantages. Patient preference for either an oral or parenteral route of administration is also pertinent. Other considerations that may influence choice of treatment include past and current comorbidities.

Second line targeted therapy

Because anti-TNFs were the first bDMARDs to become available, if a patient experienced an inadequate response to the first anti-TNF, a second agent in class could be tried and clinical trials subsequently confirmed observational data that a proportion of patients failing to respond to a first anti-TNF will attain a response to a second agent, whether administered after a delay [89] or

immediately as in the EXXELERATE trial which confirmed highly similar efficacy and safety on comparing two different anti-TNFs, certolizumab pegol and adalimumab, both administered with background MTX [90]. As a general rule, the level of efficacy with any targeted therapy is less when used after a first TNFi failure than when used as a first line bDMARD. Both ACR and EULAR recommend switching to a non-TNF bDMARD or a tsDMARD if a second TNFi fails [85,74].

Non-pharmacotherapeutic management

The importance and value of a multidisciplinary approach to the management of established RA has already been emphasised and a detailed discussion of this broad topic is beyond the scope of this chapter. However, in brief, it is important to recognize that pharmacological intervention represents only one aspect of the management plan for RA at any given stage of disease, irrespective of its severity. Other important aspects of the total management plan include patient education, and where necessary, psychological and employment counselling. The optimum quality of life and functioning can be supported by a realistic evaluation of the most appropriate level of rest and exercise and coping with activities of daily living. In this respect, appropriate access to splints, aids, and adaptations can help preserve function and maintain independence and mobility. Counselling and information about access to social and financial benefits is also of great importance. Appropriate comfortable footwear and proper care of the feet, particularly in those patients with established deformities, can help maintain mobility and comfort. Surgical treatment may also play an essential role in relieving intractable pain and may help restore physical functioning and mobility lost as a result of mechanical damage to joints and associated structures. Surgery may also be invaluable in the treatment of secondary complications of joint disease, such as peripheral nerve entrapment at the wrist or elbow, and cervical cord compression in relation to instability of the cervical spine.

Summary

The clinical spectrum of established RA is heterogeneous, with a wide variation in age of first presentation to the rheumatologist, degree of joint involvement, and severity. If it remains active, as the disease becomes more established and time passes, structural damage becomes a major determinant of functional disability. In a proportion of patients systemic and extra-articular features may be observed during the disease course. Delayed rheumatological referral is associated with less favourable long-term outcomes. Multi-disciplinary teamwork is key to the success of a holistic approach to patient care and addressing issues related to RA that are important to the person.

Pharmacological management of established RA aims to optimally suppress the inflammatory component of the disease with an ideal treatment target of remission. But once established, a target of low disease activity may be more realistic, and the physician and patient need to work together to determine what is achievable for that individual with a view to minimise symptoms and signs, prevent progression of joint damage, preserve and improve function, while preventing and treating co-morbidity and reducing RA-associated mortality. Closely aligned to these goals include the overarching aim of restoration and maintenance of a quality of life that permits the individual to pursue normal work, domestic, and social activity.

Practice points

- A careful evaluation of RA disease activity should be undertaken by means of a validated composite score. Become familiar with one of these measures and use it consistently in regular follow up to assess therapeutic response and then adjust treatment with a view to attaining the lowest disease activity score possible without incurring unacceptable toxicity.
- Patient-centred treatment should involve setting shared treatment goals with respect to what matters most to individuals living with RA.
- PROs can be used in established RA to complement disease activity as a treatment target and with a view to informing management decisions about appropriate interventions. These may involve non-pharmacological therapy and involvement of appropriate members of the multi-disciplinary team.
- Evaluation for comorbidity should be a crucial part of the medical assessment.
- It is essential to establish good co-ordination of patient care between physicians in primary and secondary care settings.

Research agenda

- A wide range of effective targeted therapies are available for established RA giving rise to broadly similar proportions of patients achieving various thresholds of efficacy measure. There is pressing need for research to identify biomarkers for response to treatment that reliably inform a therapeutic choice.
- Research is needed to investigate whether target therapies with distinct mechanisms of action differentially modulate symptomatic features of inflammation such as, for example, pain and fatigue.
- While the overall benefit:risk of targeted therapies is broadly comparable at a population level, there are differences in terms of less common adverse event profiles. More research is needed to understand how best to mitigate toxicity in potentially susceptible individuals and how the presence of comorbidity risk factors can be used to inform treatment choice.

Conflict of interest statement

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