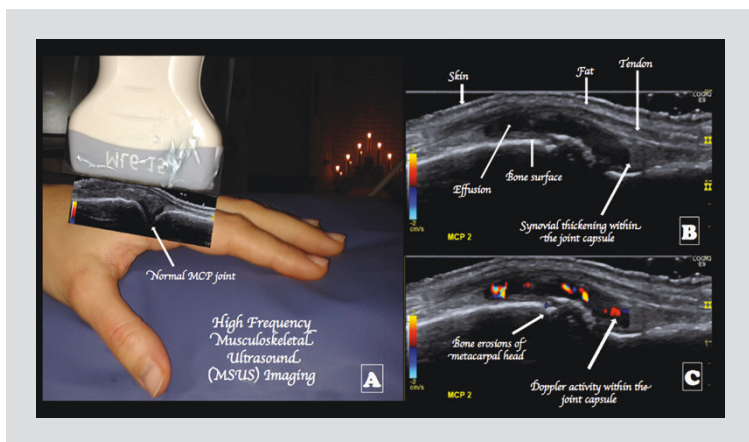


# General treatment aspects

## Goals of treatment

Rheumatoid arthritis (RA) is almost invariably associated with significant symptomatology. In the early stages of the disease, joint pain and stiffness are the dominant symptoms, but patients also frequently experience general symptoms due to the systemic inflammatory state. Extreme fatigue and lassitude, and even slight fever and profound weight loss are not unusual at this stage. The musculoskeletal symptoms may already in the earlier phase engender significant functional impairment and restriction of activities which are, however, still reversible. At later stages of the disease, inflammatory symptoms may continue to be severe but in contrast to more benign musculoskeletal conditions RA has the potential to cause severe and irreversible damage to the anatomical structures of the joints as well. Thus, erosions and other damage to the bony surfaces of the joints, and cartilage break-down are hallmarks of the disease that when advanced are easily recognized on plain radiographs, but that may at even earlier stages be detected through more sensitive imaging techniques such as magnetic resonance imaging (MRI) and ultrasound (Figure 2.1).

Importantly, these irreversible structural changes do not start late during the disease process, even though they are often only detected after months or years. Several lines of investigation strongly suggest that the destructive process starts around the same time as the onset of inflammatory symptoms [1–3]. A small subset of patients with RA have a disease phenotype that is striking for its limited symptoms despite very obvious



**Figure 2.1** Ultrasound image of the joint, demonstrating the inflammatory process in the synovium as well as an early erosive change. Photo courtesy of Y Kisten.

signs of inflammation (synovial swelling of the joints) and destructive potential seen on radiographs. This disease phenotype is referred to as the ‘robustus’ type and patients in this situation may be undertreated as a result of the limited subjective symptoms [4].

From the above follow the treatment goals for RA. First, the patient’s symptomatic burden must be alleviated. Patients generally see this as the most obvious and clearest goal of the treatment and will seek medical care primarily to obtain such relief. However, the important second goal must be to prevent, as much as possible, the destruction of joint structures as a result of the disease; these two goals are not always aligned. Simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) may provide some symptomatic relief but there is no evidence that they prevent joint damage. Even glucocorticoids (GCs) may, despite their strong anti-inflammatory and symptom-relieving properties, not prevent damage if used at moderate or high doses as monotherapy for RA (however, adding low-dose GCs to conventional antirheumatic treatments can provide some additional protection from damage, as will be discussed). Thus, the approach to RA must always be based on the dual goals of relieving symptoms and preventing long-term damage and resulting disability. These goals can be regarded as part of the more

extensive framework articulated by Fries [5], who identified the five dimensions of treating chronic illnesses as the ‘five D’s’:

- death: preventing mortality;
- discomfort: relieving symptoms;
- disability: preventing functional decline;
- drug side effects: minimizing toxicities due to the treatment; and
- dollar cost: finding an appropriate health–economic balance.

In the case of RA, while mortality that is directly attributable to the disease is rare it has been shown that patients die earlier than expected from otherwise unremarkable causes, mostly cardiovascular disease [6,7], malignancies [8], and infections [9]. A contribution to these risks from both the disease itself and the treatments seems plausible, as is the belief that more effective therapies used in a judicious manner might even improve mortality.

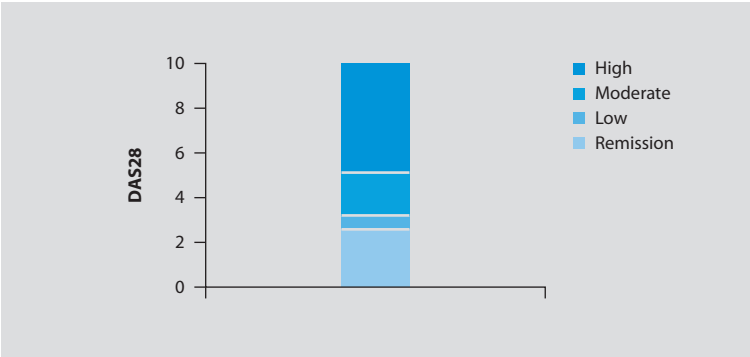
In addition to the goals of limiting discomfort and disability, the therapeutic discussions around RA are frequently dominated by considerations of the risks from the treatments, and of costs. In fact, for biologic therapies the latter aspect has become one of the dominant themes in articulating treatment approaches for RA. Thus, having good symptom-relieving properties and having demonstrated superior abilities to prevent joint damage, the use of biologics is mostly limited by some risk considerations (but having a safety profile that compared with conventional agents is good) and by the major cost issues that their use entails.

## Measuring disease activity and treatment response

### Measuring disease activity

Measuring disease activity in a chronic disease such as RA is not a trivial exercise. From the patient’s perspective the disease is multi-dimensional to begin with, causing various forms of subjective suffering: pain, stiffness, fatigue, lassitude, and a great many different kinds of disability. From the physician’s point of view disease activity may be perceived as objective signs of joint swelling, findings on imaging that represent inflammation directly (Doppler signal on ultrasound) or indirectly (juxta-articular osteopenia on plain radiographs), or as laboratory tests that vary with inflammatory states (acute phase reactants, leukocytosis,

anemia, and thrombocytosis). For practical reasons as well as for clinical research and clinical trials it has been considered advantageous to have a single value to indicate disease activity – even while respecting the multi-dimensional nature of the disease. The most widely used method for this has been the Disease Activity Score (DAS), originally developed in the Netherlands [10]. It combines four measures: the swollen joint count, the tender joint count, the patient’s global assessment, and an acute-phase reactant, into a single numerical value; the higher the value, the greater the disease activity. Several different versions of the DAS exist: the original DAS was based on a 44-joint score for swollen joints and the Ritchie articular index for tenderness, and the erythrocyte sedimentation rate (ESR), while the DAS28 uses swollen and tender joint counts based on 28 joints [11]; and either of these two can be modified to use the C-reactive protein (CRP) instead of the ESR [12]. There are also publications using a modified DAS with only three of these four components. The most widely used version, however, is the DAS28 with four components including the ESR and for this version many detailed analyses have been done. Thus, a value over 5.1 is considered a high disease activity, between 3.2 and 5.1 moderate disease activity, between 2.6 and 3.2 low disease activity, and below 2.6 a remission and these cut-offs were not simply chosen but benchmarked based on rheumatologists’ treatment decisions (Figure 2.2) [13].



**Figure 2.2 Rheumatoid arthritis disease activity based on the disease activity score using the 28 joint count (DAS28).** Cutoffs are at 2.6, 3.2 and 5.1.

However, the DAS28-based definition of remission has been criticized for allowing patients to be classified as being in remission while having several swollen and/or tender joints, violating the face validity of a remission. In defense of the DAS28 instrument, it is fair to point out that the definition may still work well at the group level if as many patients with values under 2.6 are not in true remission as there are patients whose DAS28 is above 2.6 when, in fact, they are in remission; something that is certainly seen in the clinic and for which many factors can be responsible.

Several other systems for measuring disease activity have been developed. The Simplified Disease Activity Index (SDAI) uses similar components to the DAS, but is simpler to calculate [14]; the Clinical Disease Activity Index (CDAI) is based on clinical parameters only [15]. Some instruments are based entirely on the patient's report, such as the Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5) [16] and the Routine Assessment of Patient Index Data-5 (RAPID-5) [17].

For ascertaining the functional impact of RA on the patient's daily life, a considerable amount of literature exists on the use of the Stanford Health Assessment Questionnaire Disability Index, usually (although technically incorrectly) abbreviated as 'HAQ' [18]. This series of 20 questions in eight categories of functioning in daily life yields a single numerical value ranging from 0 for full physical function to 3.0 for extreme disability. For all its limitations (floor effects, ceiling effects, subjectivity, and course-graining among other considerations) the HAQ has proven to be an exceptionally useful instrument in clinical trials and even in clinical practice [19]. A slight modification of the lay-out of the HAQ (but not of the instrument itself) that is available in Sweden has made it much easier to score so that a rheumatologist can calculate the HAQ during the patient visit with hardly any loss of time. Various modified versions of the HAQ have also been developed and used in some settings [20,21]. A more extensive assessment of physical function as well as other patient-centered domains of health and disease impact is afforded by the SF-36 [22]. The simple EuroQuol5D (EQ5D) has been developed as a measure of overall health-related quality of life (HR-QOL; utility) [23]. Finally, the instrument called 'patient-reported outcome measurement system' or PROMIS [24] is an ambitious and forward-looking initiative to integrate

item response theory and computerized adaptive testing into a clinically useful instrument, with interesting results to date [25,26].

## Measuring treatment response

It is not trivial to ascertain whether a patient has responded to antirheumatic treatment. Conventional disease-modifying antirheumatic drugs (cDMARDs) usually have a slow onset of action, measured in weeks to months. As the natural variability of the disease over time is quite considerable physician and patient recall cannot be relied upon accurately to determine if an improvement has occurred and, if so, how great it has been. During the second half of the 20th century many systems were devised to measure RA disease activity, and by the early 1990s this had led to considerable chaos in the area of therapeutics, with dozens of measurements being used in clinical trials. To address this issue, concerted efforts were made to identify the most reliable outcomes for determining whether a therapeutic was effective. Thanks to this work, it was determined that a core set of seven RA-related variables was useful: the number of swollen joints, the number of tender joints, the patient's own assessment of disease activity by a visual analog scale (VAS), the patient's assessment of pain by a VAS, the physician's assessment of disease activity by a VAS, the HAQ disability index, and an acute phase reactant for which either the ESR or the CRP could be used (Box 2.1) [27]. Based on these seven core set variables a system for ascertaining response to treatment was developed and adopted by the American College of Rheumatology (ACR): an improvement by at least 20% in both swollen and tender joints, and in at least three of the remaining five core outcomes, would identify the patient as a 'responder' according to what was called the 'ACR20 response criterion' [28]. The ACR20 was shown to have outstanding metric properties and to be able to distinguish the response to an active compound from a placebo better than any of the individual components or other plausible measures. Note, however, that the ACR20 response was not intended to reflect a clinically important or even clinically meaningful change, nor was it intended for use in clinical practice. Analogous improvements called ACR50 and ACR70 were later added and used extensively in clinical trials. Many experts feel that the

### Box 2.1 | Historical vignette

By the early 1990s, a great number of measurements were used both in clinical practice and in clinical research. In addition to measures that are still in use today, such as joint counts and visual analog scales, more fanciful measurements were also used. Some rheumatologists used systems consisting of rings of increasing diameter to measure the swelling of each joint. Some immersed the patient's finger in a mercury bath to determine the exact volume of the swollen digit. Functional tests include times for buttoning a shirt, walking a specified distance, or for performing other tasks. Hand strength was measured with various gadgets. When a task force of the American College of Rheumatology was convened to determine how best to conduct clinical trials in RA, they counted more than eighty different measurements. It is a good thing they were able to reduce it to the 'ACR core set' of just seven outcomes.

latter measures represent more clinically relevant improvements, but the differentiation from placebo is not as good for these outcomes as it is for the ACR20.

A completely different method of ascertaining response to treatment was based on the DAS28 and adopted by the European League Against Rheumatism (EULAR) [29]. The EULAR response is based on both the interval change in the DAS28 and on the DAS28 value achieved at the end of the observation period. Thus, a patient is said to have a EULAR good response if her/his DAS28 has improved by at least 1.2 and if the DAS28 after treatment is below 3.2. A EULAR moderate response is defined as having an improvement by at least 0.6 and a DAS28 after treatment below 5.1 (with a small additional modification). Compared with the ACR20, the EULAR definition of response has some attractive features, being a little more intuitive and clinically relevant, but it may not be as sensitive for detecting treatment effects in placebo-controlled trials as the ACR20 criteria. In addition, because it has three levels of response, it can sometimes be unclear what is measured most optimally.

More recently, the explicit goal of therapy in RA has been identified as remission [30]. The definition of ‘remission’ has been the subject of much work, leading to an ACR/EULAR definition that presents two possibilities: a combination of four criteria that have to be fulfilled or an SDAI<3.3 (Table 2.1) [31].

The criteria definition requires that the patient has at most one swollen and at most one tender joint, a CRP that is no higher than 10 mg/L, and registers at most 1 cm on a 0–10 cm VAS scale for the patient’s own global assessment. Each of these four criteria has to be fulfilled, combining them with the Boolean operator ‘AND’, and for this reason they are sometimes referred to as ‘the Boolean remission criteria’ [31]. Recent studies have pointed at some weaknesses with the definition, especially

<b>American College of Rheumatology/European League Against Rheumatism definitions of remission in rheumatoid arthritis clinical trials*</b>
<b>Boolean-based definition</b>
At any time point, patient must satisfy all of the following: Tender joint count ≤1 <sup>†</sup> Swollen joint count ≤ <sup>†</sup> C reactive protein ≤1 mg/dl Patient global assessment ≤1 (on a 0–10 scale) <sup>‡</sup>
<b>Index-based definition</b>
At any time point, patient must have a Simplified Disease Activity Index score of ≤3.5 <sup>§</sup>
*See text and tables 2 and 3 for recommendations regarding assessment of remission in clinical practice settings.
<sup>†</sup> For tender and swollen joint counts, use of a 28-joint count may miss actively involved joints, especially in the feet and ankles and it is preferable to include feet and ankles also when evaluating remission.
<sup>‡</sup> For the assessment of remission we suggest the following format and wording for the global assessment questions. Format: a horizontal 10cm visual analog or Likert scale with the best anchor and lowest score on the left side and the worst anchor and highest score on the right side. Wording of question and anchors: For patient global assessment, ‘Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?’ (anchors: very well–very poor). For physician/assessor global assessment, ‘What is your assessment of the patient’s current disease activity?’ (anchors: none–extremely active).
<sup>§</sup> Defined as the simple sum of the tender joint count (using 28 joints), swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale) and C reactive protein level (mg/dl).

**Table 2.1 American College of Rheumatology/European League Against Rheumatism definitions of remission in rheumatoid arthritis clinical trials.** Reproduced with permission from © BMJ Publishing Group & European League Against Rheumatism, 2011 All rights reserved. Felson et al [31].



the fact that the VAS of the patient can sometimes be higher due to reasons other than RA [32]. It should be noted that the remission criteria were designed first and foremost for use in clinical trials, that is, for use in analyses at the group level. The criticism that some patients may not fulfill the criteria although they are in remission, or that conversely they do fulfill the criteria while a sensible rheumatologist considers them not to be in remission, is therefore not entirely relevant: as long as these two groups of patients ‘cancel out’, the definition could still work well at the group level. On the other hand, because the ACR/EULAR criteria were developed with the explicit goal of minimizing ‘false-positives’, that is, to make the group who fulfill the criteria but are not deemed to be in remission as small as possible, it is possible that group-level analyses using these criteria will yield proportions of patients who are considered in remission that are smaller than clinical reality. In this regard, the DAS28-based remission definition may yet turn out to provide the more accurate estimates.

## Overview of treatment approaches

### **Evolution of treatment approaches over the past two decades**

Until the late 1980s, treatment options were limited with only a few specific antirheumatic agents in use. These agents were all slow-acting, and some were associated with risks of major toxicities (for example, gold salts and penicillamine). Therefore, the general approach was summarized as ‘go low, go slow’. It was recommended to start treatment with acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs) and to allow a long period of time (1–2 years) to determine if this treatment was adequate. If this treatment was not adequate, smaller dosages of the specific antirheumatic therapies were initially recommended and an escalation of the treatment was only suggested after relatively long trial periods at each step. Antirheumatic medications were to be administered as single therapies and never in combination. A visualization of this approach to therapy was the ‘pyramid’ approach of treating RA: the base of the pyramid consisted of modalities that would apply to all patients including physical therapy, rehabilitation, and simple analgesics; above that came ASA and the NSAIDs; the next step upward, applicable to a

smaller proportion of patients, consisted of the DMARDs (then referred to as slow-acting antirheumatic agents, SAARDs); and the top of the pyramid consisted of rarely-used and/or experimental therapies for RA, such as plasmapheresis. To the sides of the pyramids were additional treatment possibilities that could be used when needed: GC injections or even GCs given orally, and rheumatologic surgery.

Several key observations made during the 1980s propelled a revision of this treatment strategy. It was recognized that irreversible damage to the articular structures occurs early in the disease course, and that DMARDs can to some extent attenuate the damage, suggesting that earlier intervention with such agents might prevent to some extent the long-term consequences of the disease. A revision of the treatment strategies was sometimes referred to as ‘remodeling’ or ‘inverting’ the pyramid [33], and the main ideas embedded in this rethinking were:

- the use of DMARDs early in the disease course;
- optimal dosages: escalating therapies more rapidly than had been customary in practice; and
- consideration of some combinations of DMARDs.

These ideas were summarized as the ‘RESCUE’ approach: rapid escalation, selective combinations, and consideration of unproven, experimental therapies [34].

As to the idea of combining DMARDs, this once controversial proposal was propelled to the foreground by several studies published in the early 1990s. Thus, a landmark trial by O’Dell et al [35] demonstrated that the combination of methotrexate (MTX), sulfasalazine (SSZ), and hydroxychloroquine (HCQ) was more effective than both MTX alone and the other two drugs combined. The trial also found toxicities, the main concern with combined DMARDs, to be manageable. Similarly, the combination of MTX and cyclosporine A (CyA) was tested in a randomized trial and found to be superior to MTX alone [36]. However, it should be noted that not all combination therapy trials were successful. A large randomized trial comparing MTX, azathioprine (AZA), and the combination of the two revealed that MTX+AZA was not more effective than MTX alone but was considerably more toxic [37]. Uncontrolled observational studies also revealed that even more aggressive combination therapies including

cytotoxic drugs were in some cases associated with considerable toxicities and were unlikely to result in additional benefit [38–40].

More recently, the combination of MTX and leflunomide was studied in a large, well-controlled trial that suggested some added benefit for this combination [41,42]. However, later observations derived from practice and/or registries raised more substantial concerns regarding toxicities (in this case, liver toxicity) [42] and this combination must be considered appropriate only under close monitoring.

## Overview of the non-biologic treatments for rheumatoid arthritis

The main non-biologic pharmacological treatment categories for RA are NSAIDs, GCs, and DMARDs.

### Non-steroidal anti-inflammatory drugs

NSAIDs are a large group of structurally dissimilar medications that share a single mechanism of action: blockade of cyclo-oxygenase (Cox), the rate-limiting enzyme in the production of pro-inflammatory prostaglandins. Based on the original discovery of the mechanism of action of ASA by Vane, Bergström and Samuelsson, these medications have been staples in the treatment of temporary aches and pains, but also in the treatment of various localized musculoskeletal conditions such as bursitis and tendonitis. They are sometimes used to treat gout, can be effective long-term medications for spondyloarthropathies, and are widely used for osteoarthritis. However, NSAIDs have a more modest role in the treatment of RA. They should not be used as the main therapy (except perhaps in the mildest of cases) but can be added to appropriate antirheumatic treatment to achieve more optimal symptom control. NSAIDs as a class share the risk of gastric toxicity, which can lead to gastritis, peptic ulcers, perforations, and bleeding, and are therefore often combined with proton-pump antagonists, histamine 2-antagonists, or misoprostol. Another approach aimed at avoiding the gastrointestinal toxicity of NSAIDs was the development of Cox-2 specific inhibitors, which would spare the gastric mucosa. Although this was indeed proven to be the case, the unexpected finding of a potentially increased cardiovascular risk greatly reduced the enthusiasm for this class of drugs.

## Glucocorticoids

GCs (corticosteroids) are highly effective in suppressing the inflammation in RA (and many other diseases) but are predictably associated with multiple side-effects if treatment is continued during longer periods of time at effective anti-inflammatory dosages. The use of GCs is therefore limited to several specific scenarios:

- High-dose GCs (0.5–1.0 mg/kg or even higher) are reserved for patients with organ- or life-threatening extra-articular complications of RA where they are usually combined with powerful immunosuppressives.
- Moderate-dose GCs (10–30 mg daily) can be used for short periods of time, for example as ‘bridging therapy’ while awaiting the onset of action of a slow-acting DMARD, or under special circumstances.
- Low-dose GCs (5–7.5 mg daily) can be added to DMARD therapy. Although such low GC dosages do not impart a noticeable anti-inflammatory effect, two randomized clinical trials showed that the addition of low-dose GCs to DMARDs enhances the latter’s efficacy and provides some protection against radiological damage [43,44].
- GC injections: when used appropriately, intra-articular GC injections can be very effective and safe, and are used widely in rheumatologic practice (Figure 2.3). A more systematic approach using multiple intra-articular injections in early RA was recently pioneered in two clinical trials from Denmark with excellent results [45,46].

## Conventional disease-modifying antirheumatic drugs

Conventional DMARDs are a heterogeneous group of pharmacological agents that were found empirically to possess antirheumatic efficacy. For most the mechanism of action is still only partially understood. The conventional DMARDs share some properties, including a slow onset of action (weeks to months, hence the older designation SAARDs), both symptom-relieving and structure-protecting efficacy and reasonable tolerability, serious potential toxicities that require monitoring through blood tests in most cases, and very low costs for these older medications. The most important DMARDs are:

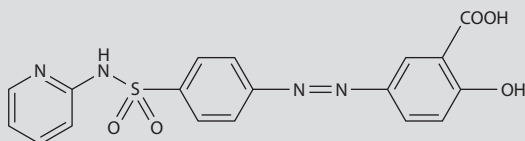
- MTX widely seen as the standard first-line therapy for RA. Originally developed as a cancer therapy, this anti-metabolite



**Figure 2.3 Intra-articular corticosteroid injection.** The proximal interphalangeal (PIP) joint is injected. Injections of inflamed small joints can provide effective relief. Photo courtesy of Professor Bent Deleuran.

(folate antagonist) was empirically shown to have a good efficacy-to-safety profile when used at low weekly dosages for chronic diseases including psoriasis, psoriatic arthritis (PsA), and RA. In an interesting twist, later research by Cronstein et al [47] strongly suggested that it is not the anti-metabolic action of MTX that determines its efficacy in RA but rather the specific enhancement of production of the anti-inflammatory endogenous mediator adenosine [48,49]. The main risks and side effects of MTX are gastrointestinal symptoms, mouth ulcers, hepatic dysfunction, and myelosuppression. MTX is teratogenic and should never be used in patients who wish to become pregnant.

- SSZ stands tall as the only DMARD originally developed for the treatment of RA. Based on what is most probably an incorrect hypothesis – that RA is caused by inflammatory changes in the gut triggered by certain bacteria – Nanna Svartz at the Karolinska Institute in Stockholm in the 1940s designed a molecule with both antibacterial and anti-inflammatory properties (Figure 2.4). SSZ showed promise in some studies but was forgotten in post-world war turbulence and only rediscovered in the 1960s when it was proven to be very effective in inflammatory bowel disease (IBD) as well as in RA. Today, it is considered a solid alternative to MTX as first-line treatment of RA, and can also be combined with MTX to achieve greater efficacy. The main risks and side effects are allergic reactions (sulfa allergy), gastrointestinal symptoms, hepatic dysfunction, and myelosuppression.



**Figure 2.4 The molecular structure of sulfasalazine.** Although based on a hypothesis that is most likely not correct, the molecule that Prof Nanna Svartz constructed and that combines the anti-inflammatory effect of acetyl-salicylic acid with a sulfa-antibiotic does have efficacy in both inflammatory bowel disease and in rheumatoid arthritis. Reproduced with permission from © SVT Bild, 2015. All rights reserved. SVT Bild [52].

- HCQ, an antimalarial agent, was serendipitously found to have antirheumatic properties. It is considered a weaker agent that is rarely used as monotherapy but can be combined with MTX and SSZ in the so-called ‘triple therapy’ regimen pioneered by O’Dell et al [50]. HCQ is generally well-tolerated but carries a very small risk for retinopathy.
- Leflunomide, a pyrimidine synthesis antagonist, was demonstrated to be as effective as MTX [51] and has similar side effects and risks, and it is therefore often a reasonable alternative to the latter. Combining leflunomide and MTX adds efficacy but at the risk of more severe toxicity [41].

### **Non-pharmacological treatments for rheumatoid arthritis**

In addition to these pharmacological therapies, non-pharmacological interventions are important in the overall management of patients with RA.

Physical therapy (physiotherapy) is recommended for all patients when the diagnosis is made and at many time points during the course of the disease. The aim must be to optimize the patient’s condition from a functional point of view, while physical therapy can also add considerably to pain control and general well-being [53]. Physical therapy is the key ingredient of medical rehabilitation for patients with RA, a large medical need for many patients that is frequently not sufficiently integrated into the care of many patients with this disease [54].

Occupational therapy can ensure that the patient benefits from the many adjustments that can be made in daily life, both in the home and at the work place, to the limitations caused by RA.

Nutritional advice is requested by many patients. The scientific basis for providing such advice is, however, rather limited. One small randomized study showed that a diet that was both gluten-free and vegan gave some improvement to the patients but was difficult to follow [55]. Another study showed that the ‘Mediterranean diet’ provided distinct benefits to patients [56]. As the latter diet is generally acceptable to the patient for the long term and is also associated with significant general and cardiovascular health benefits, at this time that may be the best practical recommendation to give to a patient with RA interested in

modifying the diet. Formal contact with a nutritionist will facilitate this from a practical point of view.

Most patients will at some point or other during the course of their disease require psychosocial support. This can be provided by different means, for example through contact with a social worker or psychologist, support groups organized through hospitals, clinics, or – most often – through the patient associations. The physician's most important contribution is to recognize when the patient is in need of such intervention and to refer or facilitate contact. Needless to say, the rheumatologist can also provide a great deal of psychological support to the patient by having an empathic and understanding attitude towards the patient with a life-long serious disease.

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