Complexities in defining remission in rheumatic diseases

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ABSTRACT

The rheumatology community has devoted increasing attention to the subject of remission over the past 2 decades, on the basis of greater appreciation of the long-term severity of inflammatory rheumatic diseases and availability of new therapies and approaches to improve outcomes. Nonetheless, description of remission in rheumatic diseases is complex, compared to many nonrheumatic diseases. Recognition of remission requires a set of measures or an index rather than a single “gold standard.” Spontaneous remission is not infrequent in people with early inflammatory arthritis, including some who may meet criteria for rheumatoid arthritis (RA) over less than a few months, and may be confused with a drug-induced remission. Remission may be transient in many patients over short periods, and the length of time required to maintain remission status varies in different reports. Maintenance of a state of remission in autoimmune diseases that result from dysregulatory processes, rather than invasion of foreign cells or toxins, generally requires ongoing therapy indefinitely. Patients who have organ damage or functional disability may be described as “in remission,” although they are free of disease activity only, but not necessarily free of disease consequences. A status of “low disease activity” or “near remission” with 70% to 90% of the features of an ideal remission may be adequate for many people with rheumatic diseases to avoid risks that may be required to reach 100% remission status. Thus, the subject of remission remains under active discussion in the rheumatology community.

Introduction

A clear indicator of dramatic changes in the therapeutic approach to patients with rheumatic diseases in recent years is the growth of interest in and reports concerning the term “remission” (1-24). Certainly, remission has always been a goal of the treating rheumatologist. However, most remissions were transient, and sustained remission was rarely observed (25). When remission was seen, it as likely represented natural variation in underlying disease processes as a result of any specific therapeutic intervention.

At this time, remission is appropriately regarded as the goal of contemporary treatment of rheumatoid arthritis (RA) (1-3, 26), and increasingly so for other rheumatic diseases. Several important developments over the past 2 decades underlie this notable change in treatment strategies, in which the goal of therapy has shifted to prevention, rather than response to, long-term damage (27): 1) The severity of long-term outcomes of rheumatic diseases, including premature mortality (28), has been increasingly recognised, with a growing awareness of the unmet needs left by traditional therapies to address adequately these conditions. 2) There has been appreciation that partial control of inflammation, as had been acceptable traditionally, often does not prevent long-term damage (29). 3) Based on progress in defining the immunopathophysiologic bases of rheumatic diseases, combined with important developments in biopharmaceutical production, new medications and combinations with greater efficacy, effectiveness, and tolerability, as well as lower toxicities than previous disease modifying antirheumatic drugs (DMARDs), have become available, with capacity to achieve complete or near-complete control of disease processes (30). 4) Evidence that severe outcomes of organ damage, such as joint destruction in RA (31) or progressive renal failure in systemic lupus erythematosus (SLE) (32) or scleroderma (33), are preventable with early aggressive intervention.

In certain situations, a status of “remission” is obvious to the patient and the clinician as “no evidence of disease” (3), a phrase long used in oncology.
However, the status of remission in rheumatic diseases may be less clear, depending not only on the disease in question but also its duration and attendant sequelae. “Remission” may not be complete in terms of recovery of function, permanent, free of organ damage, and/or free of a need to continue long-term medications to maintain remission status. Therefore, a definition of remission in rheumatic diseases can be quite complex, as presented in the 18 chapters in this supplement. This introductory chapter presents a brief summary of some of these complexities:

1. Absence of single “gold standard” measurement – the need for multiple measures or indices

Quantitative assessment of rheumatic diseases is constrained by the absence of a single “gold standard” measure, not only to establish a diagnosis, but perhaps more importantly to estimate prognosis, and to assess and monitor disease activity and response to treatment. Thus, there is not a single measure analogous to blood pressure in hypertensive patients, serum cholesterol in hyperlipidemic patients for diagnosis, monitoring, prognosis, and outcomes (34). Lacking a single measure, multiple measures or pooled indices (35) are used to determine if patient status is improved or worsened, or to define remission (16).

Classification criteria for RA (36), as well as the initial ACR remission criteria involve multiple measures (37). More recently, indices for assessment of RA (38–40), osteoarthritis (41), SLE (42), ankylosing spondylitis (43), vasculitis (44, 45), and psoriatic arthritis (46) have been developed, which may address inflammatory activity, or organ damage, or both activity and damage (a damage index is not available in RA other than radiographic scores). The need for multiple measures or indices is an important matter in approaches to remission in rheumatic diseases.

2. Spontaneous remission is not uncommon in patients who present with early arthritis

As long ago as the 1960s, it was recognised that people who met criteria for RA in population-based studies often did not meet these criteria 5 years later, and many had no disease at all at 5-year review (47, 48). In the Tecumseh cohort, a re-examination of 66 subjects who had met criteria of likely or probable RA 3 to 6 years earlier indicated 19 (29%) who continued to meet criteria for RA, 12 (18%) who met criteria for “possible RA” (49), 9 (14%) who had positive rheumatoid factor only, and 26 (39%) who had no signs of the disease (47). In the Sudbury study, a re-examination of 40 subjects 3 to 5 years after baseline indicated that only 21 (53%) of subjects who had met American Rheumatism Association (ARA) criteria for definite RA, and only 11 (15%) of those who had met criteria for probable RA, still had evidence of disease (48). At least a few subjects, perhaps the majority, who did not meet criteria for RA at the second evaluation had experienced an apparent spontaneous remission, probably as a result of recovery from a transient viral or posttraumatic arthritis, misclassification at baseline, or other basis.

Recent data from early arthritis clinics support the notion of spontaneous remission as a not infrequent event in people who have early inflammatory arthritis (50). Development of RA was more likely after 1 year. Anticyclic citrullinated protein (anti-CCP) antibodies and the shared epitope are major risk factors for persistent disease (23, 50).

Among the first 1,000 patients in the Leiden early arthritis clinic, 10% met criteria for RA, and one third presented with an undifferentiated arthritis (51). Among 1,064 patients with early arthritis, 330 were in remission after 1 year of follow-up and were discharged from the clinic (52). Similar results were seen in other early arthritis cohorts (53). In the Norwich Arthritis Register (NOAR), 42% of 358 patients with early arthritis had “natural remission” after 2 years of follow-up (54). In Birmingham, 55% of 112 patients with undifferentiated arthritis had a natural remission after 1 year of observation. In Leeds, 13% of patients were in remission after 1 year of follow-up (55).

These data suggest that spontaneous remission may be seen in 13% to 55% of individuals with undifferentiated arthritis and even among people who have clinical features of RA. It is not possible to perform placebo-controlled trials in patients who might have RA, as ethical considerations cannot permit damage (56), which may occur with a delay of 3 months (8; 57). However, it may be different in very early undifferentiated arthritis, even if disease of some of the patients might develop into RA. In these individuals, a placebo control might not be unethical and may even be necessary, since there is a high rate of spontaneous remissions. Many patients with early arthritis in whom a diagnosis of RA cannot be established would not receive DMARDs but rather symptomatic therapy and/or low-dose glucocorticoids. Indeed, many of these patients might not even be seen by a rheumatologist but are recruited in the context of early arthritis actions or clinics. We cannot appreciate sufficiently the possible risks of over-treatment versus those of under-treatment at this time. Otherwise, any interpretation of remission in patients with early arthritis, particularly when attributed to interventions, would have to recognise (and actually estimate) a certain, though unknown and potentially high, level of spontaneous remission.

3. What is the time-frame required to designate remission status?

A time-frame for remission is important. The term “remission-inducing drugs” was derived originally from evidence that some patients entered into apparent remission status when treated with traditional DMARDs, such as gold salt injections or penicillamine. However, most of the apparent remissions did not last longer than a few months, as only 2% of remissions were sustained over 3 years or longer (25).

Many patients with RA and other inflammatory diseases may experience a disease-free status without medication for 3, 6, or even 12 months, but usually not indefinitely (58, 59). As noted, such “honeymoon” phases tend to be more common and longer among patients with early disease. Furthermore, women with RA and several other rheumatic diseases, such as psoriatic arthritis,
may experience an apparent remission during a pregnancy, which generally is transient, as postpartum flares are common (60, 61).

Controversy exists about the length of time a patient must maintain a status free of disease activity to be designated as “remission.” A definition of sustained remission depends in part on the frequency of disease activity assessment itself, as sustained remission would be more likely to be reported on the basis of annual, compared to monthly, assessments. The period required to meet criteria for remission has been suggested to be as short as 2 months or as long as 2 years.

4. Can one have remission in the absence of medication?
The prototypical drug treatment in the minds of the public, including most people with rheumatic diseases and even many health professionals, involves antibiotic treatment of infections. In such situations, the patient is a host to an invading microorganism which can cause severe symptoms and even death. The treatment paradigm calls for administration of appropriate antibiotic therapy, and when the patient recovers, no further drug therapy is needed. This concept of a disease-free and drug-free state is widely regarded as an appropriate goal.

Treatment of cancer generally does not involve a self-limited process (unless immune surveillance is an ongoing phenomenon). However, a patient may enjoy a disease-free status after completion of courses of chemotherapy (and possibly radiation) without a need for further medication. Again, this remission status, with no symptoms and no medication, appears ideal.

Rheumatic diseases do not involve abnormal cells, as in infections and cancer, but rather a dysregulation of normal cells with abnormal signals to overproduce or underproduce appropriate amounts of proteins, such as cytokines. Many other chronic diseases, such as hypertension or diabetes, result from dysregulation rather than foreign cells or toxins. Treatments available at this time for dysregulatory diseases are not directed to correct the cause of the dysregulation, which remains poorly understood, but rather to the consequences of the dysregulation, such as inflammation in RA, or hyperglycemia, hypertension, or hyperlipidemia.

“Tight control” of activity in dysregulatory diseases, such as diabetes, hypertension, and hyperlipidemia and inflammatory rheumatic diseases, prevents organ damage and prolongs survival (32, 33, 62-66). Nonetheless, a “cure”, without a need for medication, is not available, and may require a therapy directed to correcting the dysregulation itself. It is possible that only a therapy directed at the cause of the dysregulation could effectively provide a “cure”.

In autoimmune diseases, such a cure may not even be possible, as the inciting stimulus that caused a genetically susceptible host to experience autoimmune reactivity may no longer be etiologically relevant. By antigenic drift, normal host antigens may be sufficient to sustain an aberrant immune response and its subsequent dysregulation. Therefore, the idea of “cure” of an inflammatory rheumatic disease at this time with drug-free and disease-free status may be unrealistic.

As noted, many patients with inflammatory rheumatic diseases may experience a disease-free status without medication for 3, 6, or even 12 months, but usually not indefinitely (58, 59). The dysregulation appears to recur as the diathesis has not been corrected. A powerful example of this problem is the recurrence of disease activity following ablative doses of chemotherapy, essentially ablating the host immune system, followed by stem cell transplant. Until therapies effectively directed to the dysregulation become available, it may be unlikely that most patients with RA or other rheumatic or other type of dysregulatory diseases will experience remission without medications.

5. Can remission occur in the presence of damage as a result of prior inflammation?
An important distinction in management of patients with rheumatic diseases involves differences in symptoms that result from inflammatory activity versus those that result from organ damage (67). In an ideal situation, a state of remission would involve the absence of both activity and damage (68). However, many patients already have damage when first seen, including many with RA and the majority with ankylosing spondylitis. Indeed, as pointed out by Zochling and Braun in this supplement (69), the current diagnosis of ankylosing spondylitis requires evidence of radiographic damage. In patients with SLE, even therapy that is highly effective at alleviating inflammation may not reverse the proteinuria consequent to renal damage.

Therefore, an unresolved matter for the rheumatology community is whether a patient can be in remission if damage is present. It is possible that, for example, levels of relatively modest American College of Rheumatology 20% improvement (ACR20) responses of 60% to 70%, rather than 90% to 100%, with biologic agents in clinical trials (70) may reflect that some patients have significant joint damage, with scores for functional disability, pain, and global status, that do not respond to even the most effective anti-inflammatory therapies (68). Patients may have no signs of inflammation, with no swollen or tender joints, normal erythrocyte sedimentation rate (ESR), and a patient global score of 0, but nonetheless have substantial deformity and limited motion on physical examination and radiographic damage.

Defining a state of remission has an inherent duality in patients with RA, and is therefore a complex concept. This complexity has been addressed in other diseases, such as SLE, by development of a variety of validated indices to assess either activity or damage (71-73). Occasional patients may experience full clinical remission regarding SLE activity but continue to experience increased creatinine levels or proteinuria as a consequence of prior renal damage, which was treated too late to be prevented or reversed. Similar situations occur in patients with RA, in whom the joints rather than the kidneys are the “organ” involved.
6. Is “near remission” or low disease activity state a reasonable goal for many patients, rather than a full remission?

Although a complete remission may appear optimal for all patients, many patients are content to have a response of being free of 70% to 90% of their symptoms, functional disability, pain, and global status, while being able to work, carry on most recreational activities, family activities, etc. (73). This situation may represent an application of the “Pareto principle” or the “80/20” rule, which suggests that 80% of results can be achieved with 20% of the effort and the final 20% of results may require 80% of the effort. In the case of patients with RA, an 80% response may be seen with 20% of the risk of therapies, while an effort to eradicate the final 20% of symptoms to gain a complete remission may incur 80% of the risk of therapies.

It is certain that the “side effects” of RA (74) and many other inflammatory rheumatic diseases are much more undesirable than the side effects of drugs used to treat these diseases, with an urgent need for intensive intervention. Nonetheless, a reasonable question is whether that intervention requires a 100% response, whether an 70% to 90% response is adequate as a reasonable target (12). Certainly, 20% or even 50% responses in general are not adequate (75), particularly with evidence in the form of radiographic progression and functional disability that may occur over time with these response levels. However, many patients may prefer a 70% to 90% response with lower risk of pharmacologic side effects, rather than 100% response (12).

A 70% to 90% response that has been described as “near remission” or “low disease activity state” (76) will vary for different patients and different physicians. While 100% control of inflammation may be appropriate for certain patients, 70% to 90% control may be satisfactory for others. Perhaps it may be inappropriate for guidelines (26) to necessarily specify that a complete remission is the only appropriate goal for all patients. Of course, patient preference is a vital component of these decisions. Nonetheless, some important indicators of future disability may not be associated with pain or discomfort, and might therefore not motivate patients to further reduce disease activity, which may require instruction from a physician.

These issues concerning remission illustrate that the matter remains complex. The chapters in this supplement are designed to help clarify these complexities. We hope the supplement meets an important current need for the rheumatology community.

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