Remission: a realistic goal in rheumatoid arthritis?

Remission is the treatment goal in rheumatoid arthritis. Clinical trials indicate that it can be reached. However, it is not a common phenomenon in real life due to many hurdles. We describe our own experience as an example to promote remission. Future vision includes a common platform to report outcomes from clinical settings.

KEYWORDS: outcomes ■ remission ■ rheumatoid arthritis

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Remission in randomized clinical trials

The FIN-RACo study was the first randomized controlled rheumatoid arthritis (RA) trial that used remission as the primary outcome measure [1]. In the FIN-RACo trial, remission was defined as the treatment goal and the primary outcome measure as early as 1993, years before the first biologic agent became available. Results of FIN-RACo were amazing: 42% of those who received a combination of conventional antirheumatic drugs (methotrexate [MTX], sulfasalazine [SSZ], hydroxychloroquine [HCQ] and prednisolone) for an active early RA were in remission 2 years after baseline, entirely without signs and symptoms of RA, and 68% met the disease activity index 28 (DAS28) remission criteria [2]. These findings indicated that remission is a realistic goal in RA even before the era of biologic agents.

A higher remission rate than that of the FIN-RACo trial has only been seen in two other trials so far [3,4]. After seeing the striking results of FIN-RACo, Finnish rheumatologists were curious whether adding a biologic agent to a combination of traditional drugs would improve results. In the NEO-RACo trial, both the comparator and the active arm involved a triple therapy plus prednisolone. The active arm was intensified with half-a-year infliximab therapy. At 2 years, >80% of patients in both arms were in DAS28 remission [3]. A Dutch pilot study called 'intensified COBRA' involved a triple therapy plus high-dose prednisolone. Infliximab was started in six of 21 patients who did not reach a treatment target [4]. At 40 weeks, 90% of the patients were in DAS28 remission.

Most randomized clinical trials (RCTs) are designed to analyze differences between active and control treatments, rather than to attain a certain clinical status such as remission. In addition to RCTs mentioned above, a few other trials have been directed to 'tight control' of inflammation according to a protocol that guides treatments according to clinical responses. These trials have documented that remission can be achieved in a large proportion of patients using effectively conventional antirheumatic drugs. The CIMESTRA trial required active use of glucocorticoid injections of all active joints. Remission rates were 59 and 54% for DAS28 remission and 41 and 35% for American College of Rheumatology (ACR) remission at 2 years in the combination and monotherapy arms, respectively [5]. In the TICORA trial, 65% of the tight control group and 16% in the control group were in remission according to DAS <1.6 [6]. In the BeSt study, 38–46% of patients in the four arms were in remission at the end of intervention [7]. In the CAMERA trial all patients received a monotherpy with MTX up to 30 mg. During 2 years of the study, 3-month remission periods were more often seen in patients in the computer-assisted monitoring group compared with a conventional follow-up group (50 vs 37% of patients) [8].

Two conclusions can be drawn from RCTs concerning remissions: a 'tight control' is a 'remission-inducing' strategy in patients with early RA; and remission can be achieved with a combination of MTX + SSZ + HCQ + prednisolone in early RA in 70–80% of patients.

Remission in real life

The QUEST-RA database that included patients who received usual care in 24 countries was analyzed for different definitions of remission in 2008 [9]. Roughly, only one out of ten patients was free of signs and symptoms of

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RA (ACR remission), and two out of ten met DAS28 remission criteria. However, remissions were not equally distributed between countries. Patients in countries with a low gross domestic product were least likely to be in remission. Less than one out of ten met the new ACR/European League Against Rheumatism (EULAR) criteria for remission [10].

Hurdles on the way to remission

Recognition of major differences in outcomes of RA in different countries suggests differences in the structure and process of the care as possible hurdles on the way to remission. Low gross domestic product of the country is associated with a lower rate of remission [11]. In fact, money from the society is needed in every step of healthcare reaching from education of health professionals, establishment and support of hospitals and clinics, to the finance of medications.

Structure and performance of the clinic may greatly influence outcomes. Conventional good care has been challenged by several studies. Conventional good care under supervision of experienced rheumatologists was proven inferior to tight structured monitoring in the TICORA trial [6], and inferior to computer-assisted monitoring in the CAMERA trial [8]. A recent evaluation of routine rheumatology care in the UK in 2002 to 2008 indicated that sufficient results are not yet achieved in routine care [12]. It appears that conventional good rheumatology care in well-resourced western rheumatology clinics is not a highway to remission, and obviously care is much less in less-resourced countries.

Individuals' resources to seek medical care are different in different environments. In addition to financial factors, those related to culture, traditions and beliefs interfere with patient compliance and adherence to medications.

A difficulty to define remission can be seen as one of the hurdles to reach remission. Organizations and individual colleagues have tried to capture remission into a definitive format but none of the proposed definitions is perfect so far. Absence of synovitis is required in most definitions. However, clinical examination is a limited measure to detect synovitis [13]. All definitions of remission involve absence of signs and symptoms that are not specific for RA but rather prevalent in an older population. In central Finland, only 15% of a community population over age 50 met the ACR definition for remission of RA [14].

Attempts to promote remission

One of the earliest visions for an active treatment strategy to achieve best possible outcomes for RA was expressed by Luukkainen *et al.* in 1978: "In our opinion gold treatment ought to be started in the early stages of RA, before the development of erosions. We are treating not only the actual inflammation of the joints but also the quality of the patient's life for many decades in the future" [15].

Visions of improved outcomes with the goal of remission grew through the 1980s and 1990s. The traditional 'pyramid' approach to management of patients with RA was replaced by promoting aggressive treatment strategies including remission [16–21].

Despite early visions, remission was a rare phenomenon even in the most advanced rheumatology clinics [22]. Traditional antirheumatic drugs, although called remission inducing, acted slowly and seldom induced remission. MTX was commonly used in too low doses, primarily orally and combinations of traditional antirheumatic drugs were rare [23]. Traditions to treat RA appear to change slowly.

The most recent attempts to promote remission include programs to increase awareness of remission as the treatment target of RA not only among rheumatologists but all other healthcare professionals and among patients [24]. Recommendations of antirheumatic drugs to treat patients with RA have been formulated [25,26]. The new ACR/EULAR classification criteria of RA aim for earlier diagnosis of RA [27]. Sets of quality indicators have been developed, to facilitate better rheumatology care.

Any attempt to promote remission to patients with RA is most welcome. However, guidelines and recommendations may work in ideal conditions rather than in the real world. For example, EULAR recommendations to treat RA simply suggest that patients with early RA should be treated with MTX monotherapy and if ineffective, a biologic agent should be added [26]. However, it has been shown that oral MTX monotherapy is sufficiently effective only in a third of patients with early RA. Therefore, two thirds of all patients with early RA would need a biologic agent. With current prices of biologic agents, this strategy will not work in the majority of countries. An effective and inexpensive combination of MTX + SSZ + HCQ + prednisolone was ignored in EULAR recommendations although it has been shown to lead to the best treatment results in early RA as indicated earlier.

At this time, remission is promoted to a larger extent than ever. The pharmaceutical industry is favorable to these initiatives with biologic agents although a minority of all patients in the world are able to use biologics at this time due to financial issues or safety concerns.

An example of a way to remission

Our own experience comes from a county hospital rheumatology unit in central Finland, Jyväskylä Central Hospital, which serves a population of 275,000 people. Each year, approximately 100 patients are diagnosed with early RA. Antirheumatic medications are started on the day of the diagnosis. According to FIN-RACo results, a combination of MTX + SSZ + HCQ + prednisolone (5 mg) is started if a patient has considerable disease activity. In milder cases, MTX + prednisolone is started. In any case, MTX is increased to full dose in 2–3 weeks, injectable MTX is also used in early RA. Swollen joints are injected with triamcinolone hexacetonice. Treatment target is early and continuous remission.

Routine clinic visits are scheduled at 3 and 6 months and at years 1, 2, 5 and 10 in all patients. Patients with continuously active disease and those who are treated with biologics are seen as often as clinically needed. At every visit the patient completes a self-report health questionnaire on a touch screen in the waiting area prior to the visit, which is available for the health professional as calculated scores and as raw data. The physician records tender and swollen joint counts on an electronic homunculus, as well as an estimate of overall disease activity. Disease activity on DAS28, patient-reported outcomes and the use of medications over time are shown on a flow sheet and time-oriented graphics, as well as comorbidities, extra-articular RA and surgeries. Radiographs of hands and feet are scheduled at 1-, 2-, 5- and 10-year visits.

Each patient is assigned to a rheumatology nurse specialist for individual patient education. The first education session is at the time of diagnosis and the second 2 weeks later, and continues at each clinic visit. Patients and relatives are invited to a group education session some months after diagnosis, as well as to a one-day course that involves lectures by multidisciplinary specialists. Patient education deals with several aspects of self-care of RA although the main focus of patient education is to inform him/her about treatment target and the importance of medications to reach this goal.

Consultation of a physical therapist is an essential part of patient education. Patients with early RA are tested for muscle strength and aerobic capacity and an individualized exercise program is planned to each patient, with control visits to a physical therapist at 1 and 2 years.

This early RA program has been developed since 1997 with prospective follow-up of patients. At a 5-year follow-up in 2002–2003, 41% were in DAS28 remission of <2.6, 34–37% were in clinical remission with no tender and no swollen joints and a normal ESR, 12–17% were in ACR remission and 55% in radiographic remission defined as no new worsening of erosions and no new erosions since baseline [28]. In a clinical evaluation of all RA patients in 2010 (one third diagnosed before 1997), 54% were in DAS28 remission [Sokka T, Haugeberg G, Asikainen J *et al*. Similar clinical outcomes in rheumatoid arthritis with more vs. less expensive treatment strategies. Results from two rheumatology clinics with standard monitoring of all patients (2011), Submitted]. Although these remission rates are among the best in usual clinical practice, space for improvement remains.

Future perspective: vision of remission continues to grow

At this time, we are closer to remission in RA than ever before. However, remission may not be achieved by blindly following general recommendations and consensuses which may work in ideal world but not in real life. Instead, remission grows from work of individual visionary rheumatologists who take into account local resources and circumstances and adjust clinical practice in individual clinics to promote remission. The mission of a clinic needs to be identified and the process of care to be adjusted to reach the goal.

Visionaries see the glass half-full, not half empty. For example, if a patient or a society cannot afford extensive use of expensive antirheumatic drugs, the game is not over. Efforts need to be directed to methods that promote remission with low costs such as fast access to care, immediate initiation of a combination of traditional antirheumatic drugs and effective patient education such as described above. Remission can be induced by traditional antirheumatic drugs and biologic agents given at right time together with an intensive patient education.

Fragmented data are available from the real-world setting of outcomes of RA including remissions. Scientific descriptive reports of individual clinics are difficult to publish, as rheumatology literature is dominated by results of RCTs. Therefore, a platform is needed to report outcomes of routine patient care from individual clinics, including rates of remission. This platform might not be on a scientific

forum but a general domain that collects outcomes data including a careful description of clinical structure and process to describe circumstances and medications in which outcomes grew. Different ways that lead to highest rates of remission in real-world settings could thus be identified and repeated by other clinics. There would be less space for 'hotel-based' medicine [29] and hotel-based recommendations [26].

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Executive summary

- Results of randomized controlled trials indicate that remission can be achieved in a majority of patients with early rheumatoid arthritis who are treated with a combination of traditional disease-modifying antirheumatic drugs.
- In usual care, a minority of patients are in remission, and very few in countries with a low gross domestic product.
- Various hurdles can be identified that prevent patients to reach remission.
- Remission has been advocated for decades, but at this time more than ever.
- A practical example of a clinic that promotes remission may help colleagues to use the same methods in their own clinic.
- Remission grows from work of individual visionary rheumatologists who take into account local resources and circumstances and adjust usual clinical practice to promote remission.

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