

“There is something you must see”: breaking down the remission concept in rheumatoid arthritis from a rheumatologist’s perspective

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Abstract Objective

To explore the remission concept in rheumatoid arthritis (RA) and the implications of the existing definitions when applied to clinical practice among rheumatologists with different profiles.

Methods

A qualitative study through focus groups was conducted. Three focus groups were organised from February to March 2016. Each group was composed of rheumatologists with extensive clinical experience with different profiles; experts in basic research (RBR), experts in imaging techniques research (RIR), and experts in clinical research (RCR). The data was collected with audio recording. Verbatim transcriptions of the audio files were made, and a subsequent reflexive thematic analysis assisted by ATLAS.ti (GmbH, Berlin, v. 7) software was performed.

Results

From the reflexive thematic analysis, three main themes were generated: (1) remission limitations, (2) instruments or measures to assess remission, and (3) a new definition of remission. Rheumatologists mentioned frequently that the following variables should be considered when developing a new remission definition: inflammatory activity, calprotectin, psychological variables, sex, disease stage, and sociocultural factors. Contrary to what could be expected, all groups acknowledged that their research field could contribute with domains for a gold standard remission instrument, but not in a hierarchical arrangement of importance. The dissonance existing in the entire remission evaluation process was outlined: remission in clinical practice versus remission in clinical trials, remission following the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Boolean versus Musculoskeletal Ultrasound (US) remission, and remission from the rheumatologist’s point of view versus the patient’s point of view.

Conclusion

Currently, rheumatologists would not accept a domain as more important than others in remission. Our suggestion is, not to generate a universal definition of remission – one that could cover all aspects – but rather to develop definitions of remission for the different settings that could be pondered by the patient’s perspective.

Key words

remission, rheumatoid arthritis, qualitative research, rheumatology

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Introduction

The treat-to-target strategy in rheumatoid arthritis (RA) has a goal defined as clinical remission or low disease activity (1, 2). In an ideal case, RA remission refers to the absence of disease symptoms and complete arrest of structural progression and functional deficit over time (3, 4). However, in clinical practice remission is complex with multiple definitions and scales coexisting, up to a point in which patients with the same activity may obtain different scores and classification (4-16). Nowadays, rheumatologists can choose among any of the following remission criteria: (i) Disease Activity Score 28 (DAS28) <2.6 , (ii) Simplified Disease Activity Index (SDAI) ≤ 3.3 , (iii) Clinical Disease Activity Index (CDAI) ≤ 2.8 , (iv) American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Boolean (28 tender joint count, 28 swollen joint count, patient's global assessment (0-10 scale), CRP (mg/dL), all ≤ 1), (v) Disease-modifying anti-rheumatic drug (DMARD)-free sustained remission; defined as the absence of sustained synovitis after cessation of DMARD therapy, and (vi) musculoskeletal ultrasound (US) remission (4, 17-20). The last one is even more complex because there are different definitions of US remission. Some authors define it as an absence of joints with power Doppler (PD) signal (6, 13, 15, 21). Others accept a more stringent definition, which requires the absence of synovitis both on a grey scale (GS) and power Doppler ultrasound (PDUS) (22). Van der Ven *et al.* (14) accept a minimal amount of synovitis on GS and define US remission as a grey-scale grade of synovitis ≤ 1 and power Doppler grade of synovitis = 0 for each scanned joint, and several authors accept a minimal residual PD signal (total PD activity score ≤ 1) (8). However, it is important to highlight that some studies have shown that clinical remission established on the basis of different indexes (DAS28, SDAI, CDAI, and ACR/EULAR Boolean) does not entirely correspond to imaging remission and some patients might experience radiographic progression despite being in clinical remission (4, 23, 24).

In addition, the Outcome Measures in Rheumatology (OMERACT) group is currently adding to the efforts and leads the initiative of redefining remission in RA taking into account the perspective of people with RA (25-30).

Despite this massive mobilisation to better define remission, a consensus definition and subsequently implementation to clinical practice is still absent. In our previous work (31), we compared remission definitions and related concepts between rheumatologists and patients, with the purpose of identifying similarities and disparities across the different perspectives. When doing the study, we noticed very different perspectives between rheumatologists, and thus now, our aim is to explore the remission concept in RA and the implications of the existing definitions when applied to clinical practice among rheumatologists with different profiles.

Methods

Study design and participants

A qualitative study through focus groups was conducted. Three focus groups were organised from February to March 2016 and were moderated by methodologists previously trained (EL, LC), who did not have any work relationship with the participants. Each group was composed of rheumatologists with extensive clinical experience with different profiles; experts in basic research (RBR), experts in imaging techniques research (RIR), and experts in clinical research (RCR). Participants were selected through purposive sampling; this type of sampling allows careful examination of the data to carry out a systematic comparison (32). The purpose of qualitative sampling is to reflect the diversity within the group or population being studied, rather than aspiring to select a representative sample (33). Our interest was to contact with nuclear subjects with a real concern and experience with the problem under study – remission in RA. The participants were contacted and invited to be part of the study via phone call by the principal investigator (MM). Their participation was formalised by the signing of an informed consent. Table I shows the characteristics of the sample.

Materials and procedure

The focus groups were conducted on different dates in the facilities of Pfizer Madrid. In these groups, in addition to the moderators, the coder (JBN) and the principal investigator were present as observer and as participant observer, respectively. Scripts with guide questions were created to be used by the moderators in each focus group. However, the scripts were not used in a strict way and the emergence of topics and issues out of the script were allowed in order to provide a safe environment for free discussion.

Data collection and analysis

The duration of each focus group was 90 minutes. Audio recorder equipment was used by the coder for data collection; in addition, field notes were taken by the moderators and were handed over to the coder after each group. The coder was responsible of transcribing the audio files. For the verbatim transcriptions and subsequent reflexive thematic analysis, ATLAS.ti (GmbH, Berlin, v. 7) software was used, for which the coder is a certified trainer (34, 35).

Data was codified following an inductive approach and was divided into first and second cycles of coding methods. The first cycle enclosed *in vivo* coding, initial coding, and/or values coding which are often recommended as a method of attuning to the participants language and perspectives. In the second cycle, data coded in the previous cycle were reorganised, recoded and analysed with pattern coding and focused coding to identify themes or explanations (36). The codification cycles finished when data saturation was achieved – 62 codes were created (coding tree) – and no new codes were created. Furthermore, and to diminish the possible bias of having a single coder, the coding tree was shared with one of the moderators (LC) who is a more experienced supervisor. The supervisor provided feedback to the coder who, after reflecting on how the data was coded, applied some changes reducing the coding tree to 48 codes (A list of all codes is available in the Supplementary file).

Results

The results are reported according to the COnsolidated criteria for Reporting

Table I. Characteristics of the sample of rheumatologists (n=18).

Profiles	n	Women	Mean age	Mean experience in years*
Experts in Basic Research (RBR)	6	3	51 (48-57)	22 (18-30)
Experts in Imaging Techniques Research (RIR)	6	3	52 (47-60)	22 (19-35)
Experts in Clinical Research (RCR).	6	2	55 (50-60)	25 (19-30)

*Years of experience in RA.

Table II. Direct quotations of main theme “Remission limitations”.

Group	Direct Quotations
RBR	The visual scale forces you to record data. It has been internalised that you need to know the number of joints... I do not know what remission by Doppler is, I only know that it correlates. ...more than a correlation is needed ...I use what I learned to use, if I use anything else I have to learn again. It is like a black box. Is not WHAT you put in, but more HOW you put it in.
RIR	... we value different things. Rheumatologists have neglected to evaluate mobility. Sometimes, if one looks at someone in remission with ACR/EULAR criteria, and then check with the images and one sees that they are not really in remission. ...remission in practice and the one considered in clinical trials should be the same, but they are not.
RCR	This is the generation of objective data. There is no problem with the Ultrasound, but there are subjective things that you need to look for. You have to know how to interpret. Reading what the radiologist says is not enough. Another problem that arises is when there is disagreement because the patient says that he/she is well, and the doctor says it is not well enough, or vice versa. We must look for what to measure, but it is very artificial.

RBR: Experts in Basic Research; RIR: Experts in Imaging Techniques Research; RCR: Experts in Clinical Research.

Qualitative research (COREQ: <http://www.equator-network.org/reporting-guidelines/coreq/>).

From the reflexive thematic analysis, three main themes were generated: (1) remission limitations – encompasses the limitations of the multiple existing remission definitions, (2) instruments or measures to assess remission – encompasses issues related to the instruments or measures currently available to assess remission, and (3) a new definition of remission – encompasses all the things that should be considered for a future remission definition.

Although all the groups agreed on the importance of these themes, discrepancies were observed between rheumatologists with different profiles.

Remission limitations

All groups of rheumatologists expressed the difficulty of reaching consensus on a definition of remission. They recognised that, in clinical practice, not all established parameters are assessed and this is a major limitation.

Despite the breakthroughs in imaging techniques, the RBR pointed out that studies supporting its role in remission usually demonstrate correlation rather than a formal validation as gold standard. However, the need to record objective data, such as those derived from imaging techniques, has been internalised by physicians. This idea worries some of the rheumatologists since it is possible that the evaluation of subjective variables that could be substantial in remission are probably not being considered: “... *there are subjective things to look for. You have to know how to interpret [images], just reading it is not enough*”. In addition, the dissonance existing in the entire remission evaluation process was outlined: remission in clinical practice *versus* remission in clinical trials, remission following the ACR/EULAR Boolean criteria *versus* US remission, and remission from the rheumatologist’s point of view *versus* the patient’s point of view.

All rheumatologists expressed the need to develop new instruments to assess

remission more effectively. However, before developing a new instrument, the construct to be measured should be better defined. The creation of a new instrument or measure brings up the concern that many rheumatologists apply in the clinical practice what they learned during their formal education, and in Spain, physicians are not required to undergo continuous education and re-certification; for so the creation of a new instrument could be interpreted as an extra training burden. Table II shows direct quotations on the theme from the rheumatologists' groups.

Instruments or measures to assess remission

Rheumatologists recognised the limitations of the instruments and measures available to assess remission. The RBR emphasised that most instruments were created in a particular historical context, but medicine is dynamic, and it changes over time, and therefore many of them have gone from being useful to being obsolete. A critique of the Disease Activity Score (DAS) was shared among the groups, agreeing that different rheumatologists may interpret it dissimilarly. However, they consider it to be a fairly acceptable tool, even more reliable than the imaging techniques. They proposed that for improving the effectiveness of the DAS, swollen joints should score more than the painful ones.

Imaging techniques, especially ultrasound, were another tool that generated debate. Several rheumatologists recognised that having an image helps patients to visualise their illness through an objective test, but like other instruments, the context should be taken into account and not validate the image by itself. Some RIR pointed out that research with ultrasound techniques contradicts itself, what brought up a performance problem that leads to validate outcomes with non-validated techniques. Interestingly, RBR rheumatologists expressed that the development of an instrument or measure that could be defined as the gold standard in remission is a task that should be on the shoulders of the RIR experts.

Different proposals on measures that

Table III. Direct quotations of main theme "Instruments or measures to assess remission".

Group	Direct Quotations
RBR	I like the rheumatoid factor, but it is complicated... The DAS problem is how it is done, and where it is done. It was created in a historical context and that context has changed and DAS has lagged behind. The DAS is absurd. Swollen joints should be scored more than the painful joints. ... measure inflammation. What happens is that it is a continuum. We are not equal to cardiologists. We do not agree on DAS among rheumatologists. In fact, biomarkers do not contribute anything, but they are used in research.
RIR	An isolated signal will generate uncertainty. The works on the topic contradict each other. There are good and bad echographers. Image depends a lot on them. A bad resonance or bad captured images are useless. DAS and SDAI are quite acceptable. I do not say that they are optimal, but they are not trash either. I would not replace them with the imaging techniques. Imaging is just as good as other instruments, but it depends on the context. I think that imaging by itself does will not displace other instruments. It would have already proved it. The ultrasound brings a performance problem: we validate things that are not really there.
RCR	We have to be careful with the findings of imaging studies that are published, because one thing are the radiologists of the studies and another very different are those who work in your hospital.
RBR: Experts in Basic Research; RIR: Experts in Imaging Techniques Research; RCR: Experts in Clinical Research.	

should be taken into consideration for the future development of a new instrument were suggested by the participants. Among them, measuring inflammation was the most highlighted, with the consequent difficulty of what cut-off use, because inflammation is a continuum. The lack of a 100% objective instrument in rheumatology, unlike other medical specialties, was exposed (See Table III).

A new definition of remission

The participants expressed that a new definition of remission should take into account the inflammatory activity. The RBR specifically pointed out the role of matrix metalloproteinase-3 (MMP3) and calprotectin as relevant biomarkers of inflammatory processes. The RIR and the RCR highlighted the importance of psychological variables, such as anxiety and depression, because they have a great weight and influence in the outcome of the disease. The debate generated two novel variable proposals to understand and assess remission: steroid-free time or the number of drugs prescribed, but they should be studied in more depth and validated.

A group of rheumatologists emphasised that a new definition of remission should arise from a previous agreement between expert and patient. RCR expressed that remission should be defined by the patient rather than by the

rheumatologists, emphasising on the importance of the patient's opinion. However, some pointed out, that in order for remission to be useful in clinical practice, it should allow corrections by age, sex, disease stage (recent onset disease vs. advanced disease), and socio-cultural factors.

Different perspectives and discrepancies among rheumatologists on what should be included in a new definition of remission became evident, but contrary to what could be expected, all groups acknowledged that their research field could contribute with domains for a gold standard, but not in a hierarchical arrangement of importance. They believed more in a horizontal symmetrical arrangement where the relevance of each research field remains to be assigned (See Table IV).

Discussion

From the reflexive thematic analysis three main themes among rheumatologists were generated (remission limitations, instruments or measures to assess remission, and a new definition of remission). However, each group paid attention to different aspects within each theme.

RBR highlighted the contemporary research on calprotectin (37-41) and identified it as the biomarker of the future. At present calprotectin is not included in any guideline and its use is limited

Table IV. Direct quotations of main theme “A new definition of remission”.

Group	Direct Quotations
RBR	MMP3 and calprotectin are fantastic because they are always present when inflammation is present. I would include calprotectin in a new definition. If we talk about remission, we are talking about inflammatory activity. ...the best measure should be an inflammation measure. ... we need to correct it by age.
RIR	... an agreement between expert and patient. We should consider the psychosocial variables. We need to talk about them freely, because they have a great influence. The psychosocial variables have a great weight. ... it can be defined as the time free of corticoids.
RCR	Each patient has his/her own point of remission. It should be defined more by the patient than by the rheumatologists. The patient should express feeling good. It is important to differentiate between long-term and recent onset patients. The mental aspects have great influence. The patient opinion is very important; it is important to make a deal [between patient and physician]. It also depends on the culture and the zone where you live. The difference in the experience of the disease depending on sex is important. Variable that has never been touched: number of prescriptions.

RBR: Experts in Basic Research; RIR: Experts in Imaging Techniques Research; RCR: Experts in Clinical Research.

to research, despite promising performance (42, 43).

For their part, RIR recognised that the current instruments have serious limitations (44-48). Imaging techniques have helped to define disease status more accurately and have become an aid to make patients better understand their disease. However, they do not recognise imaging techniques as an instrument capable of being the gold standard in remission, but rather as a tool to reinforce existing instruments and measures.

On the other hand, RCR emphasised that a new definition of remission should arise from a previous agreement between expert and patient. They identified the doctor-patient relationship and effective communication as core elements in assessing remission. This coincides with previous studies that demonstrate that patient confidence in their physician is a predictive factor of acceptance or rejection in decision making regarding care in RA (49, 50). This group also relegated the importance of instruments of objective measures and highlighted the relevance of subjectivity to identify remission. They indicated that it is possible that “each patient has his/her own point of remission”.

Despite highlighting different aspects related to remission, all groups agreed on the importance of psychosocial variables in the disease course and during

treatment evaluation. This shows a breakthrough in medicine, where psychological variables tend to be ignored and biological variables – biomarkers and imaging techniques – have become the main focus. This vision coincides with the current definition of health proposed by the World Health Organisation: *Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity* (51).

Our findings demonstrate the ambiguity in the definition, criteria, tools and measures available to assess remission in RA. This ambiguity has been demonstrated in previous research (6-10, 12, 15, 16, 25, 52-55), and forces the rheumatology community to develop new measures or instruments that allow a more accurate evaluation of remission in RA. We should emphasise that for the development of a tool that can be considered the gold standard in remission we might need to think out of the box (31) since previous approaches have failed to reach a wide consensus. A proposal that may reduce the existing dissonance between perspectives – remission in clinical practice *versus* remission in clinical trials, remission following the ACR/EULAR Boolean criteria *versus* US remission, and remission from the rheumatologist’s point of view *versus* the patient’s point of view

– could be defining remission for different purposes *e.g.* specific definitions of remission according to setting.

From our data, we can extract that the development of a new tool should consider the following variables: (i) inflammatory activity, (ii) calprotectin, (iii) psychological variables, (iv) sex, (v) disease stage and (vi) sociocultural factors. Currently, rheumatologists would not accept a domain as more important than others. Our suggestion is, not to generate a universal definition of remission – one that could cover all aspects – but rather to develop definitions of remission for the different settings that could be pondered by the patient perspective.

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