

VIEWPOINT

Timing the therapeutic window of opportunity in early rheumatoid arthritis: proposal for definitions of disease duration in clinical trials

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ABSTRACT

The effects of treatment in early rheumatoid arthritis (RA) and the consequences of delayed therapy represent important areas for research. The concept of a 'window of opportunity' is now well established and considerable attention has been paid to when it might close. However, in order to study how long the window of opportunity lasts, the timing of its opening must be precisely defined. An analysis of definitions of 'onset' in clinical studies reveals imprecision and heterogeneity, making accurate assessment of this important concept of the 'window of opportunity' very difficult. In this paper we propose that, in clinical trials in early RA, data on durations since onset of symptoms and onset of joint swelling as well as disease duration based on fulfilment of classification criteria should be routinely presented.

There has been considerable interest in whether the earliest clinically apparent phase of rheumatoid arthritis (RA) represents a genuine therapeutic window of opportunity. Although the potential mechanisms underlying an early window remain controversial, its existence is now widely accepted.^{1,2} Debate has surrounded when the 'window' closes although the 'first 3 months' are now often suggested to be a key period.³

A focus on when the window closes has been at the expense of careful consideration of what we mean by 'onset', or the point from which we should time its opening. Onset can be defined in a number of ways including: (1) onset of any symptom attributable to RA; (2) onset of joint swelling; (3) fulfilment of classification criteria for RA; (4) time of clinical diagnosis of RA by a qualified physician. For an individual patient, it is highly unlikely that all these 'onset' dates will be the same.

An analysis of definitions of 'onset' in clinical studies reveals imprecision and heterogeneity, which makes accurate assessment of the 'window of opportunity' very difficult. In general, studies addressing the 'window of opportunity' concept take one of the following forms. First, cohort studies looking at the impact of intervention commenced 'early' versus 'late'.⁴⁻¹⁵ Second, clinical trials in which patients were randomly assigned to early versus delayed disease-modifying antirheumatic drug interventions,¹⁶ or subanalyses of clinical trials in which response was assessed in relation to symptom duration at the initiation of treatment.¹⁷⁻¹⁹ Third, early 'aggressive' pharmacological

intervention versus early 'non-aggressive' pharmacological intervention in which the long-term impact of a more intensive initial strategy was compared with the long-term impact of a less intensive initial strategy, after a period in which treatment was equivalent between groups.²⁰⁻³⁰

Across these different study designs (details of studies referred to are given in supplementary Table S1, available online only), the definitions of 'onset' vary considerably and include the:

- onset of 'symptoms'^{5 6 8-14 19 25 26 28 29}
- time of the patient's first reported joint swelling^{7 15}
- time of fulfilment of classification criteria²⁸
- time of 'diagnosis'.^{17 21 27}

For some studies, intervals from two different definitions of 'onset' have both been detailed.^{21 27 28} However, for many studies it has not been possible to determine from which point onset was timed.^{4 16 18 20 22-24 30} The most frequent definition of 'onset' related to the onset of symptoms. While what the investigators would allow as an 'RA symptom' was rarely defined, in some cases investigators were explicit about the loose definition used ('symptom onset as defined by the patient').¹⁰ Equivalent heterogeneity is seen in definitions of disease duration in studies that have addressed treatment outcomes in 'early' RA without focussing on whether outcomes of early treatment are better than those of late treatment; indeed in many it is not detailed at all from when 'disease duration' was timed.³¹⁻³⁴

This analysis highlights the difficulty of comparing between different studies reporting outcomes of interventions in early RA. Figure 1 illustrates the journey of a theoretical patient whose disease course is characterised by 3 months of arthralgia, morning stiffness and fatigue, followed by the onset of arthritis, which eventually, after a further 3 months, evolves such that classification criteria for RA are fulfilled. The situation is further complicated by the fact that the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria³⁵ are often fulfilled earlier than the 1987 criteria,³⁶ and so even time from fulfilment of classification criteria can vary widely depending on which criteria are used.³⁷ Depending on how 'disease onset' is defined, studies looking at treatment 'within the first 3 months' may actually be looking at interventions applied at entirely different times in the patient's journey.

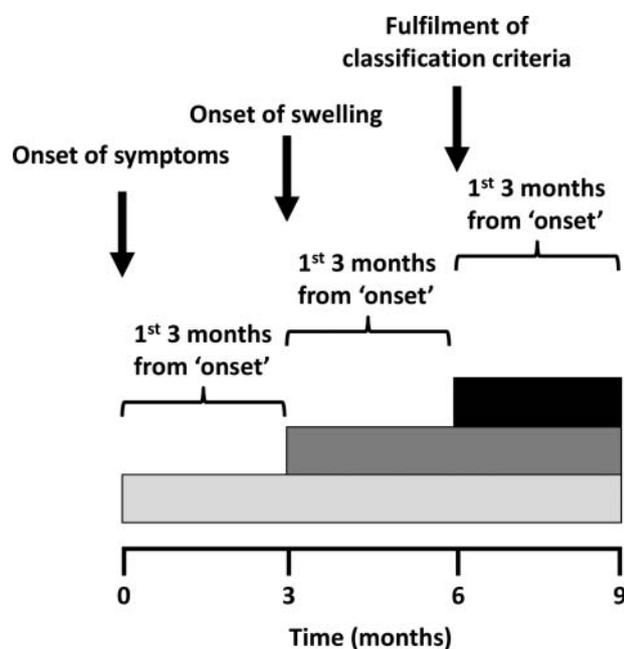


Figure 1 Schematic representation of what might be meant by the 'first 3 months' from onset depending if 'onset' is taken from the onset of symptoms (pale grey), joint swelling (dark grey) or fulfilment of classification criteria (black).

Recognising some of these issues, the EULAR Study Group for Risk Factors for Rheumatoid Arthritis has recently made recommendations that, when possible, the following dates should be systematically recorded for patients entering clinical studies of early RA:³⁸

1. First musculoskeletal symptoms relevant (in the opinion of the assessing rheumatologist) to the current complaint.
2. First persistent (ie, chronic until presentation) patient-reported joint swelling.
3. Initial fulfilment of criteria for RA (1987 ACR³⁶ and 2010 ACR EULAR)³⁵ based on data obtained retrospectively from the patient's history.
4. Initial fulfilment of criteria for RA (1987 ACR and 2010 ACR EULAR) based on the rheumatologist's assessment.

Regarding date (3) for the 1987 criteria, the tree format allows the substitution of clinical variables for the results of investigations (rheumatoid factor/hand and wrist radiographs). Fulfilment of these criteria is thus possible to establish based solely on the patient's history. For the 2010 criteria the situation is different. For items A ('joint involvement') and D ('duration of symptoms') we suggest that these data could be obtained from the patient's history. For items B ('serology') and C ('acute phase reactants') we recognise that the classification criteria are explicit that 'at least one test result is needed for classification'. Consequently, patients could be classified retrospectively according to the 2010 criteria only if results of investigations were available from a previous assessment (eg, by a family doctor/general practitioner).

Investigators in clinical studies and trials can clearly choose whatever point they wish to define 'onset'. However, we propose reporting the interval from each of the dates above till enrolment into the study, and as secondary outcomes looking at the relationships between each 'duration' and the clinical outcome(s) under consideration. This approach will lead to greater clarity about patient characteristics and will facilitate comparisons between studies.

A number of aspects of the EULAR recommendations regarding the timing of 'onset' remains imprecisely defined and requires further research to inform them. This is particularly the case for the onset of the 'first musculoskeletal symptoms relevant (in the opinion of the assessing rheumatologist) to the current complaint'.³⁸ An important area for consideration in the context of this is whether one should record the date of the first palindromic (in the case of palindromic symptoms) or the date of the first symptoms that were continuous till presentation. Importantly, the 2010 ACR/EULAR classification criteria for RA are explicit that the duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (eg, pain, swelling, tenderness) of joints that 'are clinically involved at the time of assessment, regardless of treatment status'.³⁵ Within this classification system, onset at a particular joint that was not involved at the time of assessment (ie, that was transient) would not be taken into account when determining 'symptom duration'.³⁵ This will thus be reflected in dates (3) and (4) in the EULAR study group recommendations. For date (1) we propose that the date of the first palindromic symptom, which may be swelling or another inflammatory joint symptom, is recorded (assuming that the rheumatologist believes that it is related to the current inflammatory arthritis). We do, however, suggest that it would be helpful for researchers to record whether the date of the 'first musculoskeletal symptoms' relates to symptoms that were palindromic or not. This will allow the subsequent assessment of differences between patients with palindromic and non-palindromic onsets. Second, it remains unclear what symptoms should be regarded as 'attributable to RA'. Symptoms a patient attributes to RA may be different to symptoms that their physician attributes to RA, and both parties may sometimes be unclear as to whether some symptoms (eg, fatigue) were actually attributable to the onset of RA. In addition, a very insidious onset of symptoms can make the identification of their 'start' difficult. More work is necessary to address these issues.

We acknowledge that there are potentially important dates whose capture has not been explicitly recommended. One such date is the date of first clinician reported joint swelling, which is likely to lie on the continuum between date (2; first persistent patient reported joint swelling) and date (4; initial fulfilment of criteria for RA based on the rheumatologist's assessment). While we do not wish to suggest that dates such as this are redundant, we recognise that currently most studies provide very limited, if any, information regarding dates of 'onset'. In making our recommendations to researchers we are keen to strike a balance between what might be ideal and what might be practical to collect in a clinical research context.

The issues discussed herein are relevant not only to therapeutic studies. Studies of biomarkers of outcome and of pathogenic processes in 'early RA' often use different starting points for their 'disease duration', or do not present data allowing the reader to determine the starting point used, limiting the ability to combine datasets. Clarity is needed for future research, and meta-analyses of existing datasets need to recognise that apparently equivalent 'disease durations' in different studies may not, in reality, mean equivalent disease durations. For now, we propose presenting data on durations since onset of symptoms and onset of swelling as well as disease duration based on fulfilment of classification criteria in clinical trials in early RA.

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Competing interests KR has received grant funding from UCB, honoraria from Pfizer and UCB and meeting expenses from Pfizer and Roche. PPT is an employee of GlaxoSmithKline, Stevenage, UK. Other authors have declared no conflicts of interest.

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