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VIEWPOINT

Window of opportunity in rheumatoid arthritis – definitions and supporting evidence: from old to new perspectives

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ABSTRACT

The therapeutic window of opportunity in rheumatoid arthritis (RA) is often referred to. However, some have questioned whether such a period, in which the disease is more susceptible to disease-modifying treatment, really exists. Observational studies are most frequently referenced as supporting evidence, but results of such studies are subject to confounding. In addition formal consensus on the definition of the term has never been reached. We first reviewed the literature to establish if there is agreement on the concept of the window of opportunity in terms of its time period and the outcomes influenced. Second, a systemic literature search was performed on the evidence of the benefit of early versus delayed treatment as provided by randomised clinical trials. We observed that the concept of the window of opportunity has changed with respect to timing and outcome since its first description 25 years ago. There is an 'old definition' pointing to the first 2 years after diagnosis with increased potential for disease-modifying treatment to prevent severe radiographic damage and disability. Strong evidence supports this concept. A 'new definition' presumes a therapeutic window in a pre-RA phase in which the biologic processes could be halted and RA development prevented by very early treatment. This definition is not supported by evidence, although is less well studied in trials. Some suggestions for future research in this area are made.

INTRODUCTION

Outcomes for patients with rheumatoid arthritis (RA) have changed dramatically over the last 25 years. These advances have been attributed to the development and use of novel disease-modifying drugs (including biologics), treat-to-target strategies resulting in better control of disease activity, and the earlier initiation of disease-modifying treatments.

The rationale behind earlier treatment initiation is that it allows modulation of biologic processes while they are in a less mature and more reversible stage.[1 2] This stage has previously been referred to as a therapeutic window of opportunity.[1 2] Nevertheless, varying definitions exist of the window of opportunity. The first mention of a window of opportunity in RA was in 1992 by Dawes and Symmons.[3] At that time it was described as 'a small window of opportunity (2 years) in which to get the disease in remission before irreversible damage is done to joints'. Since then, the term 'window of opportunity' has been increasingly used in the rheumatological literature. However some have questioned whether such a period, in which the disease is more susceptible to disease-modifying treatment, really exists, and formal consensus on the definition of the term has never been reached.

In this Viewpoint we set out to propose a definition of the 'window of opportunity' based on data obtained from the literature. First we questioned whether or not the term 'window of opportunity' has been used in a consistent way since 1992. To address this, we reviewed the literature on articles that used the term 'window of opportunity' in the context of RA. We explored whether there was consensus in terms of the long-term outcomes that were considered to benefit from early treatment, as well as on the time period, expressed as the symptom or disease duration, that was proposed to cover the window of opportunity. Second, we determined the level of evidence for the association between the timing of intervention and the disease outcomes that were identified in the first part. Although a previous literature review concluded that prolonged symptom duration at treatment initiation in patients with classified RA is associated with more radiographic progression and a lower chance of achieving disease-modifying antirheumatic drug (DMARD)-free sustained remission (findings that may support the presence of a window of opportunity), this conclusion was largely driven by findings from observational cohort studies.[4] In such cohort studies, the timing of DMARD

start was not determined by randomisation. Therefore, a combination of patient and environmental characteristics, both known and unknown, may have influenced when DMARD therapy was initiated. Because of this, the causality of the associations with symptom duration is susceptible to confounding and reverse causation bias. Randomised controlled trials (RCTs) do not have this drawback. Therefore we systemically searched the literature on RCTs evaluating the effect of early (vs delayed, thus initial treatment with placebo) treatment with DMARDs. We exclusively concentrated the present literature search on findings from RCTs. We studied RCTs performed in patients with classified RA. Moreover, as the field of RA has moved towards identifying patients in earlier disease phases, in the current search we also performed RCTs performed in patients with undifferentiated arthritis (UA) and arthralgia without clinically apparent arthritis.

Is there consensus on how to define the window of opportunity?

A generic search on PubMed on (‘((rheumatoid arthritis) AND window of opportunity)’) resulted in 89 articles; evaluation of full texts revealed 75 relevant articles (both original articles as well as other types of papers) on the window of opportunity.

Timing of the window of opportunity

In 37 of 75 (49%) articles, no exact duration of the window of opportunity was included in the description; these articles often used general terms, like ‘early’. Other articles did not include a chronological period, but a disease phase, such as the phase preceding radiographic damage (two articles)[5 6] or preceding RA development (five articles).[7–11] With regard to studies that mentioned a specific time duration, some studies described the window to encompass the first 2 years after disease onset (nine articles).[3 6 10 12–17] As illustrated in figure 1A, these articles were mainly written in the 1990s and early 2000s. The most frequently used time description period encompassed the first 12 weeks or 3 months after symptom onset (19 articles)[1 4 6 10 12 18–31]; the majority of these papers were published after 2010 (figure 1A). Hence, as time has passed, the window of opportunity has been assumed to be confined to a shorter period occurring in an earlier phase of the disease.

Long-term outcomes

Twenty-six out of 75 articles (35%) used general terms with regard to the long-term outcomes that could be achieved when treatment is started within the window of opportunity (eg, ‘sustained clinical benefits’ or ‘better outcomes’). The most frequently mentioned specific outcome was prevention or slowing of radiographic damage (40 articles).[3–6 10 12–18 22 24 26 30–54] The second most frequently mentioned outcome was remission, either clinical remission, Disease Activity Score (DAS) remission or drug-free remission (22 articles).[1 10 15 16 18 19 22 24–26 31 34 46 48 49 55–61] Furthermore, six articles mentioned that treatment within the window of opportunity could result in cure[6 14 29 30 49 62] of RA, and six articles even mentioned prevention of RA as the outcome of treatment within the window of opportunity.[7–11 61] As shown in figure 1B, these latter outcomes were present in more recent descriptions of the window of opportunity.

In conclusion, the definition of the window of opportunity as was retrieved from the literature revealed that the concept has changed over time. Whereas it was previously defined as a treatment period in the first 2 years after disease onset in which joint damage could be halted (‘old definition’), it is increasingly considered to represent a period before the diagnosis is established in which treatment could potentially prevent RA development (‘new definition’).

EVIDENCE OBTAINED FROM RANDOMISED CLINICAL TRIALS IN FAVOUR OF EARLY TREATMENT

Next, in order to determine the level of evidence of the associations that are the basis of these definitions, we systematically assessed databases (PubMed, Medline, Embase) for RCTs that compared early versus delayed treatment with DMARDs in different disease phases (RA, UA and arthralgia preceding clinical arthritis) (see online supplementary methods for used terms). Patients in all these phases required to be DMARD-naïve at trial entry. Delayed treatment was defined as absence of DMARD use for a certain period. Hence an early treatment group was compared with a group that only used placebo (please see online supplementary methods for the inclusion and exclusion criteria that were used). The quality of all included studies was determined using a 15-point quality list that was adapted from lists previously used in systematic reviews[4 63] (online supplementary tables 1 and 2). As previously,[4] studies with a quality score ≥75% were considered high-quality studies. Due to heterogeneity in study designs, pooled effect estimates were not calculated, but a best-evidence synthesis was performed, based on the method described by the Cochrane Collaboration Back Review Group (online supplementary table 3).[64]

RCTs in early RA

First we searched the literature for RCTs in early RA (disease duration <2 years) comparing early DMARD initiation with non-DMARD therapy or delayed DMARD therapy. A total of 11 trials were identified, all published between 1988 and 2003 (table 1); 9 trials assessed the outcome radiographic damage[17 65–72] and 8 functional disability.[17 65 69–74]

Radiographic damage in RA

All nine RCTs included DMARD-naïve patients with a disease duration of <2 years who fulfilled the classification criteria for RA (either the 1958 or the 1987 criteria) (table 1). Follow-up ranged between 6 months and 5 years. Different DMARDs (gold, sulfasalazine, hydroxychloroquine, methotrexate [MTX] and prednisone)

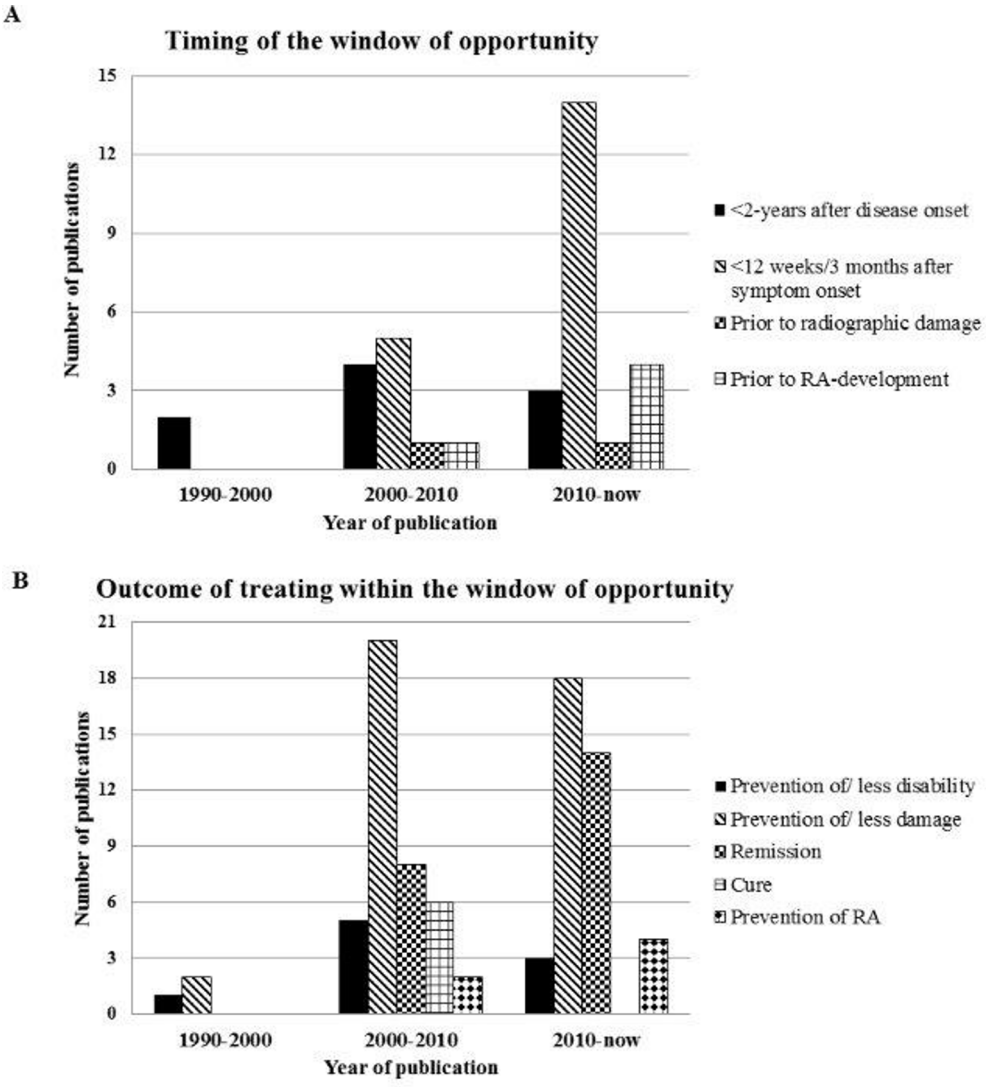

Figure 1 Results from literature search on the concept of the window of opportunity in rheumatoid arthritis (RA) with regard to its time period (A) and long-term outcome that is influenced (B). The bars correspond to the number of times a specific time period or long-term outcome was mentioned in the 75 articles mentioning the window of opportunity in RA. As some articles mentioned more than one time period or outcome, and other papers did not mention a specific time period or outcome at all, the numbers in the bars do not necessarily add up to 75.

and different measures for radiographic damage (Larsen score, [modified] Sharp score, presence of erosions and erosion area) were used. A significant benefit for the early DMARD arm with regard to radiographic damage was shown in five RCTs,[17 65 68 70 71] of which three were of high quality[17 65 70] (two of these reported on the same trial).[17 65] Three RCTs showed a statistically non-significant benefit for the early DMARD arm,[66 67 69] and in one trial there was no effect.[72] Since there were consistent findings in multiple high-quality RCTs (as well as in low-quality RCTs), there is strong evidence to conclude that early DMARD initiation results in better radiographic outcomes (figure 2). Importantly, earlier treatment resulted in lower absolute levels of joint damage and in lower progression rates (ie, less steep progression curves over time).[17 65 70] Especially the latter finding of less rapid rise over time is suggestive of true disease modification. With respect to timelines, the early treatment group in these trials started DMARDs ~6–12 months earlier than the delayed group (table 1).

Functional disability

All eight RCTs that measured functional disability as outcome (table 1) included DMARD-naïve patients fulfilling the classification criteria for RA (1958 or 1987) with a disease duration <2 years. Follow-up ranged between 36 weeks and 5 years. Different measures of functional disability were used (Health Assessment Questionnaire, Keitel Functional Index, Arthritis Impact Measurement Scales and McMaster-Toronto Arthritis Patient Preference Disability Questionnaire). Seven of the RCTs were of high quality. However, four different study populations were described, as three articles were long-term follow-up papers of previously reported study populations.[17 72 74] Four out of seven high-quality studies revealed a significant benefit for the early DMARD arm,[17 65 69 73] of which

Table 1 Overview of placebo-controlled trials comparing early versus delayed DMARD initiation in early RA looking at radiographic joint damage and disability

First author, year of publication	Type of trial	Quality score* (%)	Patients	N	Follow-up time	Intervention	Control	Outcome of interest	Relevant result	Association between early DMARD intervention and outcome
Radiographic damage										
Borg, 1988[65]	Randomised, double-blind, placebo-controlled trial.	80	Definite or classical RA (1958 criteria), symptoms <2 years, active disease.*	132 (67/65)	2 years	Auranofin 6 mg daily.	Placebo 6 mg daily. Median delay to DMARD start 12 months.	Larsen.	Auronafin arm: median increase Larsen score 6.0 → 13.0. Placebo arm: median increase 9.5 → 21.5. Difference between groups p<0.05.	S
The Australian Multicentre Clinical Trial Group, 1992[66]	Randomised, double-blind, placebo-controlled trial.	60	Probable, definite or classical RA (1958 criteria), disease duration <12 months, no erosions.*	105 (52/53)	6 months	SSZ 2000 mg daily.	Placebo 2000 mg daily. Delay to DMARD start unknown.	Positive or negative for erosions on X-rays of the hand and feet.	After 6 months, 12% of patients had erosions in the hands, 10% in the feet. 'A tendency towards a statistically significant difference between groups with SSZ group.	NS
Hannonen, 1993[67]	Randomised, double-blind, placebo-controlled trial.	73	Definite RA (1958 criteria), disease duration <12 months, active disease.*	78 (38/40)	48 weeks	SSZ 2000 mg daily.	Placebo 2000 mg daily. Delay to DMARD start unknown.	Modified Sharp score.	Mean increase in radiological score (erosions + joint space narrowing): 3.5 in SSZ arm vs 7.1 in placebo arm (p=0.13).	NS
Buckland-Wright, 1993[68]	Randomised controlled trial.	27	Diagnosis of RA, disease duration <2 years.*	29 (13/16)	18 months	Gold 50 mg/week + NSAIDs.	Delayed Gold 50 mg/week (after 6 months) + NSAIDs.	Erosion area.	First 6 months, significant increase in both groups, second 6 months a lower proportion in Gold group had erosion area progression (p<0.005). Third 6 months decrease in erosion area in both groups.	S
Egsmose, 1995[17]†	Randomised, double-blind, placebo-controlled trial.	80	Definite or classical RA (1958 criteria), symptoms <2 years, active disease.*	75 (40/35)	5 years	Auronafin 6 mg daily.	Placebo 6 mg daily. Median delay to DMARD start 12 months.	Larsen.	At 5 years, the Larsen score in the placebo arm had reached values roughly twice those in the auronafin arm (p=0.004).	S

Continued

Table 1 Continued

First author, year of publication	Type of trial	Quality score* (%)	Patients	N	Follow-up time	Intervention	Control	Outcome of interest	Relevant result	Association between early DMARD intervention and outcome
van der Heide, 1996[69]	Randomised controlled trial.	80	1987 RA, disease duration <1 year.*	238 (181/57)	12 months	HCQ 400 mg/day or intramuscular Gold 50 mg/week or MTX (up to 15 mg/week).	NSAIDs. Possibility to start DMARDs after 12 months.	Modified Sharp score.	Mean increase in radiological damage score: +7 in DMARD arm vs +8 in control group (not statistically significant).	NS
Choy, 2002[71]	Randomised, double-blind, placebo-controlled trial.	73	1987 RA, disease duration <1 year, active disease.*	117 (62/55)	12 months	SSZ 2000 mg daily + placebo diclofenac.	Diclofenac 100 mg daily + placebo SSZ. Delay to DMARD start unknown.	Erosions, assessed by Sharp method.	Mean number of new erosions in SSZ arm 2.0 vs 7.5 in diclofenac arm (p=0.002).	S
van Everdingen, 2002[70]	Randomised, double-blind, placebo-controlled trial.	87	1987 RA, disease duration <1 year, active disease.*	81 (40/41)	2 years	Prednisone 10 mg/day.	Placebo 10 mg/day. Possibility to start DMARD after 6 months.	Modified Sharp score.	Mean change in modified Sharp score: 16 prednisone vs 29 in placebo arm (p=0.007).	S
Verstappen, 2003[72]*‡	Randomised controlled trial.	80	1987 RA, disease duration <1 year.*	189 (145/44)	5 years	HCQ 400 mg/day or intramuscular Gold 50 mg/week or MTX (up to 15 mg/week).	NSAIDs. Possibility to start DMARDs after 12 months.	Sharp/van der Heijde.	Mean increase Sharp/van der Heijde score per year 7.3 for intervention arm vs 6.8 for control arm (not statistically significant).	NS
Functional disability										
Borg, 1988[65]	Randomised, double-blind, placebo-controlled trial.	80	Definite or classical RA (1958 criteria), symptoms <2 years, active disease.*	132 (67/65)	2 years	Auronafin 6 mg daily.	Placebo 6 mg daily. Median delay to DMARD start 12 months.	HAQ. Keitel Functional Index.	Median change in HAQ score: −0.17 in intervention arm vs −0.02 in control arm (p<0.05). Median change in Keitel index −5 in intervention arm vs 1 in control arm (p<0.01).	S
Egsmose, 1995[17]†	Randomised, double-blind, placebo-controlled trial.	80	Definite or classical RA (1958 criteria), symptoms <2 years, active disease.*	75 (40/35)	5 years	Auronafin 6 mg daily.	Placebo 6 mg daily. Median delay to DMARD start 12 months.	HAQ. Keitel Functional Index.	After 5 years, differences in HAQ score (p=0.08) and Keitel index (p<0.006) in favour of intervention arm.	S

Continued

Table 1 Continued

First author, year of publication	Type of trial	Quality score* (%)	Patients	N	Follow-up time	Intervention	Control	Outcome of interest	Relevant result	Association between early DMARD intervention and outcome
The HERA Study Group, 1995[73]	Randomised, double-blind, placebo-controlled trial.	93	1987 RA, disease duration <2 years, active disease.*	119 (59/60)	36 weeks	HCQ up to 400 mg/day.	Placebo up to 400 mg/day. Possibility to start DMARD therapy after 24 weeks.	Physical function index (combination AIMS, HAQ and MACTAR).	At 36 weeks, there was significant benefit for the HCQ arm in the physical function index (p=0.020).	S
van der Heide, 1996[69]	Randomised controlled trial.	80	1987 RA, disease duration <1 year.*	238 (181/57)	12 months	HCQ 400 mg/day or intramuscular Gold 50 mg/week or MTX (up to 15 mg/week).	NSAIDs. Possibility to start DMARDs after 12 months.	HAQ.	Mean change in HAQ score –0.4 in intervention arm vs –0.1 in control arm. Mean difference 0.3 (95% CI 0.2 to 0.6).	S
Tsakonas, 2000[74]*†§	Randomised, double-blind, placebo-controlled trial.	93	1987 RA, disease duration <2 years, active disease.*	115 (58/57)	45 months	HCQ up to 400 mg/day.	Placebo up to 400 mg/day. 9-month delay to DMARD start.	Physical function index (combination AIMS, HAQ and MACTAR).	After 45 months, mean change in physical function index –0.48 in intervention arm vs –0.40 in control group (no p value given).	NS
Choy, 2002[71]	Randomised, double-blind, placebo-controlled trial.	73	1987 RA, disease duration <1 year, active disease.*	117 (62/55)	12 months	SSZ 2000 mg daily + placebo diclofenac.	Diclofenac 100 mg daily + placebo SSZ. Delay to DMARD start unknown.	HAQ.	No clinically relevant changes in HAQ score were observed within or between groups.	NS
van Everdingen, 2002[70]	Randomised, double-blind, placebo-controlled trial.	87	1987 RA, disease duration <1 year, active disease.*	81 (40/41)	2 years	Prednisone 10 mg/day.	Placebo 10 mg/day. Possibility to start DMARD after 6 months.	HAQ.	Mean change in HAQ after 24 months: 0.1 in intervention arm vs 0.0 in control arm (p>0.2).	NS
Verstappen, 2003‡	Randomised controlled trial.	80	1987 RA, disease duration <1 year.*	189 (145/44)	5 years	HCQ 400 mg/day or intramuscular Gold 50 mg/week or MTX (up to 15 mg/week).	NSAIDs. Possibility to start DMARDs after 12 months.	HAQ.	Mean change in HAQ score after 5 years of follow-up: –0.20 in intervention arm vs –0.12 in control, not statistically significant.	NS

*Studies with a quality score ≥75% were considered to have high-quality scores.
†This study reports on the same population as the study by Borg *et al*.[65]
‡This study reports on the same population as the study by van der Heide *et al*.[69]
§This study reports on the same population as the study by the HERA Study Group.[73]
AIMS, Arthritis Impact Measurement Scales;DMARD, disease-modifying antirheumatic drug;HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; MACTAR, McMaster-Toronto Arthritis Patient Preference Disability QuestionnaireMTX, methotrexate; NS, not significant;NSAIDs, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; S, significant; SSZ, sulfasalazine.

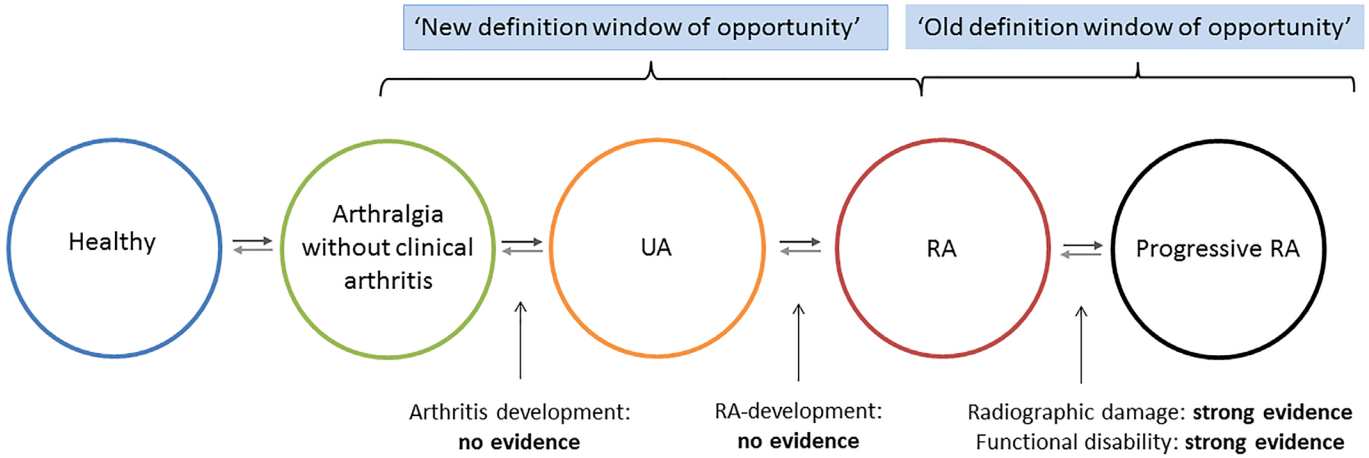

Figure 2 Summary of evidence for randomised controlled trials on the effect of early versus delayed treatment with disease-modifying antirheumatic drugs per disease phase. RA, rheumatoid arthritis; UA, undifferentiated arthritis.

two reported on the same population.[17 65] Of the other three high-quality studies, two reported a non-significant benefit for early treatment.[72 74] The early group started DMARDs ~6–12 months earlier than the delayed group. Because of consistent findings in multiple high-quality RCTs, there is strong evidence for early DMARD initiation with regard to improved functional outcome (figure 2).

RCTs in UA aiming to prevent RA development

Next the literature was searched for RCTs in patients with UA (online supplementary methods). Six articles, reporting on five RCTs, compared DMARD treatment with placebo treatment in patients with UA (table 2). Different definitions of UA and inclusion criteria were used (table 2). Follow-up durations ranged between 1 and 5 years, and different DMARDs were investigated (MTX, infliximab, methylprednisolone and abatacept). The outcome was RA according to the 1987 criteria for RA[75–78] or the clinical diagnosis.[79 80] Four RCTs were of high quality.[76 77 79 80] None of the trials reached a significant difference in the primary outcome, but all four high-quality studies showed a tendency towards less RA development in the DMARD arm. Interestingly a recent meta-analysis of trials in patients with UA or very early RA by Hilliquin *et al*[81] did show a significant risk reduction on RA development in the case of DMARD initiation in a pre-RA phase when all trials were combined in one analysis.[81] Nonetheless there is no conclusive evidence from individual RCTs that early treatment in patients with UA prevents progression to RA as none of the individual trials revealed a significant reduction (figure 2).

A difficult issue here is that the outcome in the trials was mostly fulfilment of the 1987 criteria, and that the concept of RA, at least with respect to classification, has changed in the last decennium.[82] Some of the patients previously considered as UA may currently be diagnosed or classified as RA. On the other hand, patients with UA with a low risk of RA were also included. As demonstrated recently, such non-informative inclusions diminish the power to detect differences[83] and may also have contributed to negative results.

Hopefully, a well-powered, placebo-controlled trial will be done in the nearby future to determine conclusively that early DMARD treatment in UA is beneficial in preventing progression to RA.

RCTs in arthralgia without clinical arthritis aiming to prevent RA development

Finally the literature was searched for RCTs (described in full papers) performed in patients considered at risk for RA development but without arthritis (online supplementary methods). One RCT was identified that included seropositive patients with arthralgia who were shared epitope-positive (table 3).[84] Patients were randomised to either dexamethasone or placebo and followed for a median of 26 months. After this period, there was no difference in arthritis development between the two arms. Thus, no evidence from RCTs yet exists for prevention of arthritis by initiating DMARD treatment in patients with arthralgia without clinical arthritis with regard to arthritis/RA development (figure 2). However, several randomised clinical trials are currently ongoing and results are awaited in the next 5 years.[7]

DISCUSSION AND FUTURE PERSPECTIVES

The term 'window of opportunity' is commonly used within the field of RA, although its definition has changed over the last 25 years. There is an 'old definition' indicating that the therapeutic window lies within the first 2 years after disease onset, and treatment within it results in less radiographic damage and disability. We have here demonstrated that there is convincing evidence for this effect based on data from RCTs, particularly when treatment was delayed for 6–12 months after diagnosis, due to the use of placebo medication during this period. Notably, earlier treatment resulted in absolute lower levels of radiographic joint destruction and in slower progression rates. Lower absolute levels were possibly

Table 2 Overview of RCTs comparing early versus delayed DMARD initiation in patients with UA in order to prevent RA development

First author, year of publication	Type of trial	Quality score* (%)	Patients	N	Follow-up time	Intervention	Control	Outcome of interest	Relevant result	Association between early DMARD intervention and outcome
van Dongen, 2007,[76] PROMPT trial	Randomised, double-blind placebo-controlled trial.	93	Probable RA (1958 criteria), not fulfilling the 1987 criteria for RA.	110 (55/55)	30 months	Up to 30 mg of MTX/week.	Up to 30 mg placebo/week.	Fulfilment of the 1987 criteria for RA.	After 30 months, 40% in intervention arm and 53% in control arm fulfilled the 1987 criteria (not statistically significant). Time to RA development significantly longer in intervention arm (p=0.04).	NS
Saleem, 2008[75]	Randomised, double-blind placebo-controlled trial.	64	Poor prognosis UA <12 months' symptom duration.	17 (10/7)	52 weeks	Infliximab 3 mg/kg for 14 weeks.	Placebo 3 mg/kg for 14 weeks.	Fulfilment of the 1987 criteria for RA.	At week 52, 17/17 (100%) of patients developed RA.	NS
Verstappen, 2010,[79] STIVEA trial	Randomised, double-blind placebo-controlled trial.	93*	Inflammatory polyarthritis small joints, symptom duration 4–10 weeks.	265 (133/132)	12 months	3× 80 mg intramuscular methylprednisolone acetate at 0, 1 and 2 weeks.	3× placebo intramuscularly at 0,1 and 2 weeks.	Clinical diagnosis of RA.	Clinical diagnosis of RA in 60.4% of patients in control arm, vs 48.6% in intervention arm (p=0.145).	NS
Machold, 2010,[80] SAVE trial	Randomised, double-blind placebo-controlled trial.	79	Inflammatory arthritis, symptom duration <16 weeks.	383 (198/185)	52 weeks	1× 120 mg methylprednisolone intramuscularly.	1× placebo (NaCl) intramuscularly.	Clinical diagnosis of RA.	Proportions of patients developing RA were similar in the intervention arm and control arm (45.1% vs 50.7%, p=0.36).	NS
Emery, 2010,[78] ADJUST trial	Randomised, double-blind placebo-controlled trial.	71	1–3/7 points 1987 criteria, arthritis ≥2 joints, ACPA-positive, symptom duration <18 months.	56 (28/28)	1 year	Abatacept ~10 mg/kg for 6 months.	Placebo ~10 mg/kg for 6 months.	Fulfilment of the 1987 criteria for RA.	At year 1, 46.2% in the intervention arm vs 66.7% in the control arm fulfilled the 1987 criteria for RA (difference −20.5%, 95% CI −47.4% to 7.8%).	NS
van Aken, 2014,[77]† PROMPT trial	Randomised, double-blind placebo-controlled trial.	93	Probable RA (1958 criteria), not fulfilling the 1987 criteria for RA.	110 (55/55)	30 months	Up to 30 mg of MTX/week.	Up to 30 mg placebo/week.	Fulfilment of the 1987 criteria for RA.	After 5 years, 45% in intervention arm and 53% in control arm fulfilled the 1987 criteria (p=0.45).	NS

*Studies with a quality score ≥75% were considered high-quality studies.
†This study reports on the same population as a previous study by van Dongen *et al*.[76]
ACPA, anticitrullinated protein antibody;ADJUST, Abatacept study to Determine the effectiveness in preventing the development of rheumatoid arthritis in patients with Undifferentiated inflammatory arthritis and to evaluate Safety and Tolerability; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; NS, not significant;NaCl, Natrium Chloride; PROMPT, probable rheumatoid arthritis treated with methotrexate or placebo; RA, rheumatoid arthritis;RCT, randomised controlled trial;SAVE, stop arthritis very early; UA, undifferentiated arthritis.

Table 3 Overview of placebo-controlled trials comparing early versus delayed DMARD initiation in patients with arthralgia considered at risk for progression to RA in order to prevent arthritis development

First author, year of publication	Type of trial	Quality score*	Patients	N	Follow-up time	Intervention	Control	Outcome of interest	Relevant result	Association between early DMARD intervention and outcome
Bos, 2010[84]	Randomised, double-blind placebo-controlled trial.	93%	ACPA-positive and/or RF-positive patients with arthralgia, without arthritis. SE-positive.	83 (42/41)	Median 26 months.	100 mg dexamethasone intramuscularly at 0 and 6 weeks.	100 mg placebo intramuscularly at 0 and 6 weeks.	Arthritis development.	After a median follow-up of 26 months, 9/42 patients in intervention arm and 8/41 in placebo arm developed arthritis (p=0.9).	NS

Only full-text articles were reviewed.
*A study with a quality score ≥75% was considered of high quality.
ACPA, anticitrullinated protein antibody;DMARD, disease-modifying antirheumatic drug; NS, not significant RA, rheumatoid arthritis; RF, rheumatoid factor; SE, shared epitope.

only the consequence of an earlier start, whereas a less steep rise in joint destruction is suggestive for true disease modification. In addition to an 'old definition', a 'new definition' is used in the literature as well. This states that the window could even lie in a phase preceding diagnosis or fulfilment of classification criteria for RA and that treatment initiated could possibly result in prevention of RA. However, this definition is not (yet) supported by evidence from RCTs.

Interpreting data from studies addressing the concept of a window of opportunity is challenging. One particular issue relates to understanding its duration. Measuring the duration of the window requires that a starting point is clearly defined. Many studies exploring the concept of a window of opportunity will simply report 'disease duration' and will conclude that treating patients with a disease duration of less than *x* months is associated with improved outcomes compared with treating patients with disease duration of greater than *x* months. However, when that *x* months is timed from is often inadequately described. Possibilities include when the patient first developed (1) inflammatory-type joint symptoms, (2) patient-reported joint swelling, (3) physician-observed joint swelling and (4) physician-documented fulfilment of the RA classification criteria.[85] Clearly adopting different definitions of a starting point for the disease onset will lead to different durations of the therapeutic window.[21] Although some recall bias may be present when collecting information about starting points, especially when this was a long time ago, specifying the different starting points using uniform definitions will promote comparability between studies and the interpretation of findings.

Another issue relates whether the concept of a window of opportunity requires that there must be a time after which it closes, that is, a time after which intervention is not as effective as it was if used during the window. Trials have used placebo regimens for defined periods of time, but the rationale for the duration of placebo treatment is never discussed. Many observational studies dichotomised symptom duration and compared outcomes; here a cut-off was frequently placed at 3 months after symptom onset. However this choice actually refers back to two observational studies revealing that treatment initiation within 3 months after symptom onset was associated with less damage and more remission; evidence for the choice of this time period was not provided and other time periods were not explored.[31 86] Thus far only one study evaluated the time course and provided suggestive evidence that a confined period in which treatment is more effective is more likely than a general 'the earlier the better' effect.[19]

In the first part of this Viewpoint, we assessed the most commonly used definitions of the window of opportunity. A limitation is that this was done by a literature search in one database. We presume that a search in more databases and also incorporating different terminology may have yielded some additional papers providing descriptions of the window of opportunity. However, we expect

that a more systematic search will not result in different conclusions regarding the long-term disease outcomes and time periods most frequently mentioned in the different time periods (as presented in figure 1). In the second part in contrast, we determined the level of evidence. Here a systematic literature search of results obtained from RCTs was required. Due to heterogeneity in study designs, meta-analyses were not possible, but a best-evidence synthesis, based on the method described by the Cochrane Collaboration Back Review Group, was performed.

The present review of the literature demonstrated that different definitions of the window of opportunity are used, of which two definitions were common. It is clarifying if subsequent studies that use the term the window of opportunity will specify which definition is meant. The current work does neither allow to make a statement about the best definition of the window of opportunity, nor determine the optimal period for starting disease-modifying antirheumatic treatment. This is subject for future studies.

CONCLUSION

In summary, while the concept of a window of opportunity in RA is widely used, different definitions of this window exist. We propose to differentiate an 'old' and a 'new definition'. The 'old definition' points to the first 1–2 years after diagnosis with increased potential for disease-modifying treatment to prevent severe radiographic damage and disability, whereas the 'new definition' presumes a therapeutic window in a pre-RA phase in which the biologic processes could be halted and RA development prevented by very early treatment. A review of RCTs revealed a high level of evidence for the 'old definition' but no scientific evidence for the 'new definition'. As there were relatively few trials performed in pre-RA phases, more research is needed to verify the new definition. Furthermore, to arrive at an evidence-based new definition of the window of opportunity, including information on its duration and possible closing, future trials should use adequately described definitions of the starting point.

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REFERENCES

1. van Nies JAB, Tsonaka R, Gaujoux-Viala C, *et al*. Evaluating relationships between symptom duration and persistence of rheumatoid arthritis: does a window of opportunity exist? results on the Leiden early arthritis clinic and ESPOIR cohorts. *Ann Rheum Dis* 2015;74:806–12.
2. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. *Arthritis Rheum* 2003;48:1771–4.
3. Dawes PT, Symmons DPM. Short-term effects of antirheumatic drugs. *Baillière's Clin Rheumatol* 1992;6:117–40.
4. van Nies JAB, Krabben A, Schoones JW, *et al*. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. *Ann Rheum Dis* 2014;73:861–70.
5. Á S, Á H, Gulyás K, *et al*. Effects of targeted therapies on the bone in arthritides. *Autoimmun Rev* 2017;16:313–20.
6. Quinn MA, Cox S. The evidence for early intervention. *Rheum Dis Clin North Am* 2005;31:575–89.
7. van Steenbergen HW, da Silva JAP, Huizinga TWJ, *et al*. Preventing progression from arthralgia to arthritis: targeting the right patients. *Nat Rev Rheumatol* 2017 https://www.nature.com/articles/nrrheum.2017.185 (cited 2017 Dec 18).
8. Lopez-Olivo MA, Kakpovbia-Eshareturi V, des Bordes J, *et al*. Treating early undifferentiated arthritis: a systematic review and meta-analysis of direct and indirect trial evidence. *Arthritis Care Res* 2017.
9. Mankia K, Emery P. A new window of opportunity in rheumatoid arthritis: targeting at-risk individuals. *Curr Opin Rheumatol* 2016;28:260–6.
10. Nam JL, Emery P. Is there a place for initial treatment with biological DMARDs in the early phase of RA? *Best Practice & Research Clinical Rheumatology* 2013;27:537–54.
11. Goronzy JJ, Weyand CM. Developments in the scientific understanding of rheumatoid arthritis. *Arthritis Res Ther* 2009;11.
12. González-Álvaro I, Ortiz AM, Seoane IV, *et al*. Biomarkers predicting a need for intensive treatment in patients with early arthritis. *Curr Pharm Des* 2014;21:170–81.
13. Keystone EC, van der Heijde D, Kavanaugh A, *et al*. Clinical, functional, and radiographic benefits of longterm adalimumab plus methotrexate: final 10-year data in longstanding rheumatoid arthritis. *J Rheumatol* 2013;40:1487–97.
14. Atzeni F, Sarzi-Puttini P. Early rheumatoid arthritis]. *Reumatismo* 2007;59:100–17.
15. Keen HI, Emery P. How should we manage early rheumatoid arthritis? from imaging to intervention. *Curr Opin Rheumatol* 2005;17:280–5.
16. Bijlsma JW, Jacobs JW. The practice guideline "Rheumatoid arthritis" (first revision) from the Dutch College of General Practitioners: a response from the perspective of rheumatology]. *Ned Tijdschr Geneeskd* 2004;148:557–8.
17. Egsmose C, Lund B, Borg G, *et al*. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. *J Rheumatol* 1995;22:2208–13.
18. Monti S, Montecucco C, Bugatti S, *et al*. Rheumatoid arthritis treatment: the earlier the better to prevent joint damage. *RMD Open* 2015;1(Suppl 1):e000057.
19. Nagy G, van Vollenhoven RF. Sustained biologic-free and drug-free remission in rheumatoid arthritis, where are we now? *Arthritis Res Ther* 2015;17.
20. Raza K, Filer A. The therapeutic window of opportunity in rheumatoid arthritis: does it ever close? *Ann Rheum Dis* 2015;74:793–4.
21. Raza K, Saber TP, Kvien TK, *et al*. Timing the therapeutic window of opportunity in early rheumatoid arthritis: proposal for definitions of disease duration in clinical trials. *Ann Rheum Dis* 2012;71:1921–3.
22. Gremese E, Salaffi F, Bosello SL, *et al*. Very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study. *Ann Rheum Dis* 2013;72:858–62.
23. Jacobs JWG. Optimal use of non-biologic therapy in the treatment of rheumatoid arthritis. *Rheumatology* 2012;51(suppl 4):iv3–8.
24. van der Helm-van Mil AHM, Posthumus MD. Early recognition of rheumatoid arthritis]. *Ned Tijdschr Geneeskd* 2011;155.
25. Söderlin MK, Bergman S. Absent "Window of Opportunity" in smokers with short disease duration. Data from BARFOT,

a multicenter study of early rheumatoid arthritis. *J Rheumatol* 2011;38:2160–8.
26. Willemze A, van der Linden MPM, le Cessie S, *et al*. The window of opportunity in ACPA-positive rheumatoid arthritis is not explained by AcpA characteristics. *Annals of the Rheumatic Diseases* 2011;70:1697–8.
27. Jack C, Hazel E, Bernatsky S. Something's missing here: a look at the quality of rheumatology referral letters. *Rheumatol Int* 2012;32:1083–5.
28. da MLMH, Laurindo IMM. Santos Neto LL dos. [Early rheumatoid arthritis: concepts]. *Rev Assoc Medica Bras* 1992 2010;56:227–9.
29. Raza K, Buckley CE, Salmon M, *et al*. Treating very early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2006;20:849–63.
30. Smolen JS, Aletaha D, Machold KP. Therapeutic strategies in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2005;19:163–77.
31. Nell VPK, Machold KP, Eberl G, *et al*. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology* 2004;43:906–14.
32. Forien M, Ottaviani S. Ultrasound and follow-up of rheumatoid arthritis. *Joint Bone Spine* 2017;84:531–6.
33. Harrold LR, Litman HJ, Connolly SE, *et al*. A window of opportunity for abatacept in RA: is disease duration an independent predictor of low disease activity/remission in clinical practice? *Clin Rheumatol* 2017;36:1215–20.
34. De Cock D, Van der Elst K, Meyfroidt S, *et al*. The optimal combination therapy for the treatment of early rheumatoid arthritis. *Expert Opin Pharmacother* 2015;16:1615–25.
35. Robinson PC, Brown MA. The window of opportunity: a relevant concept for axial spondyloarthritis. *Arthritis Res Ther* 2014;16.
36. Hwang YG, Moreland LW. Induction therapy with combination TNF inhibitor and methotrexate in early rheumatoid arthritis. *Curr Rheumatol Rep* 2014;16.
37. Kyburz D, Finckh A. The importance of early treatment for the prognosis of rheumatoid arthritis. *Swiss Med Wkly* 2013;143.
38. Breedveld F. The value of early intervention in RA—a window of opportunity. *Clin Rheumatol* 2011;30:33–9.
39. Kyburz D, Gabay C, Michel BA, *et al*. The long-term impact of early treatment of rheumatoid arthritis on radiographic progression: a population-based cohort study. *Rheumatology* 2011;50:1106–10.
40. Ngian G-S. Rheumatoid arthritis. *Aust Fam Physician* 2010;39:626–8.
41. Klarenbeek NB, Allaart CF, Kerstens PJSM, *et al*. The best story: on strategy trials in rheumatoid arthritis. *Current Opinion in Rheumatology* 2009;21:291–8.
42. Massardo L. Early rheumatoid arthritis]. *Rev Med Chil* 2008;136:1468–75.
43. Nurmohamed MT, Dijkmans BAC. Are biologics more effective than classical disease-modifying antirheumatic drugs? *Arthritis Res Ther* 2008;10.
44. Valesini G, Di Franco M, Spinelli FR, *et al*. Induction of remission in rheumatoid arthritis: criteria and opportunities. *Rheumatol Int* 2008;29:131–9.
45. Sherrer Y. Abatacept in biologic-naïve patients and TNF inadequate responders: clinical data in focus. *Curr Med Res Opin* 2008;24:2283–94.
46. Cush JJ. Early rheumatoid arthritis - is there a window of opportunity? *J Rheumatol Suppl* 2007;80:1–7.
47. Choy EHS, Smith CM, Farewell V, *et al*. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. *Ann Rheum Dis* 2008;67:656–63.
48. Fukuda T. Window of opportunity for treatment of rheumatoid arthritis]. *Nihon Rinsho Jpn J Clin Med* 2007;65:1276–81.
49. Yamaguchi Y, Yamamoto K. New therapeutic strategy of rheumatoid arthritis to reach the goal of suppression of joint destruction]. *Clin Calcium* 2007;17:463–73.
50. Finckh A, Liang MH, van Herckenrode CM, *et al*. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: a meta-analysis. *Arthritis Rheum* 2006;55:864–72.
51. Finckh A, Gabay C, Guerne P-A. Review of the protective effects of tumor necrosis factor inhibitors in rheumatoid arthritis]. *Rev Med Suisse Romande* 2004;124:547–50.
52. Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. *Clin Exp Rheumatol* 2003;21(5 Suppl 31):S154–7.
53. Bresnihan B. Are synovial biopsies of diagnostic value? *Arthritis Res Ther* 2003;5:271–8.
54. Geletka R, St Clair EW. Treatment of early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2003;17:791–809.
55. Espinoza F, Fabre S, Pers Y-M. Remission-induction therapies for early rheumatoid arthritis: evidence to date and clinical implications. *Therapeutic Advances in Musculoskeletal* 2016;8:107–18.
56. Contreras-Yáñez I, Pascual-Ramos V. Window of opportunity to achieve major outcomes in early rheumatoid arthritis patients: how persistence with therapy matters. *Arthritis Res Ther* 2015;17.
57. Her M, Kavanaugh A. Advances in use of immunomodulatory agents—a rheumatology perspective. *Nat Rev Gastroenterol Hepatol* 2015;12:363–8.
58. Greisen SR, Schelde KK, Rasmussen TK, *et al*. CXCL13 predicts disease activity in early rheumatoid arthritis and could be an indicator of the therapeutic `window of opportunity'. *Arthritis Res Ther* 2014;16.
59. Resman-Targoff BH, Cicero MP. Aggressive treatment of early rheumatoid arthritis: recognizing the window of opportunity and treating to target goals. *Am J Manag Care* 2010;16(9 Suppl):S249–58.
60. Thomas D. Management of patients with rheumatoid arthritis]. *Ther Umsch Rev Ther* 2005;62:281–4.
61. Furst DE. Window of opportunity. *J Rheumatol* 2004;31:1677–9.
62. Quinn MA, Emery P. Potential for altering rheumatoid arthritis outcome. *Rheum Dis Clin North Am* 2005;31:763–72.
63. Kwok WY, Plevier JWM, Rosendaal FR, *et al*. Risk factors for progression in hand osteoarthritis: a systematic review. *Arthritis Care Res* 2013;65:552–62.
64. van Tulder M, Furlan A, Bombardier C, *et al*. Updated method guidelines for systematic reviews in the Cochrane collaboration back review group. *Spine* 2003;28:1290–9.
65. Borg G, Allander E, Lund B, *et al*. Auranofin improves outcome in early rheumatoid arthritis. Results from a 2-year, double blind placebo controlled study. *J Rheumatol* 1988;15:1747–54.
66. Sulfasalazine in early rheumatoid arthritis. The Australian multicentre clinical Trial Group. *J Rheumatol* 1992;19:1672–7.
67. Hannonen P, Möttönen T, Hakola M, *et al*. Sulfasalazine in early rheumatoid arthritis. a 48-week double-blind, prospective, placebo-controlled study. *Arthritis & Rheumatism* 1993;36:1501–9.
68. Buckland-Wright JC, Clarke GS, Chikanza IC, *et al*. Quantitative microfocal radiography detects changes in erosion area in patients with early rheumatoid arthritis treated with myocrisine. *J Rheumatol* 1993;20:243–7.
69. van der Heide A, Jacobs JW, Bijlsma JW, *et al*. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. *Ann Intern Med* 1996;124:699–707.
70. van Everdingen AA, Jacobs JWG, Siewertsz van Reesema DR, *et al*. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: Clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. *Ann Intern Med* 2002;136.
71. Choy EHS, Scott DL, Kingsley GH, *et al*. Treating rheumatoid arthritis early with disease modifying drugs reduces joint damage: a randomised double blind trial of sulphasalazine vs diclofenac sodium. *Clin Exp Rheumatol* 2002;20:351–8.
72. Verstappen SMM, Jacobs JWG, Bijlsma JWJ, *et al*. Five-year followup of rheumatoid arthritis patients after early treatment with disease-modifying antirheumatic drugs versus treatment according to the pyramid approach in the first year. *Arthritis & Rheumatism* 2003;48:1797–807.
73. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA study. *Am J Med* 1995;98:156–68.
74. Tsakonas E, Fitzgerald AA, Fitzcharles MA, *et al*. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. *J Rheumatol* 2000;27:623–9.
75. Saleem B, Mackie S, Quinn M, *et al*. Does the use of tumour necrosis factor antagonist therapy in poor prognosis, undifferentiated arthritis prevent progression to rheumatoid arthritis? *Ann Rheum Dis* 2008;67:1178–80.
76. van Dongen H, van Aken J, Lard LR, *et al*. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2007;56:1424–32.
77. van Aken J, Heimans L, Gillet-van Dongen H, *et al*. Five-year outcomes of probable rheumatoid arthritis treated with methotrexate or placebo during the first year (the prompt study). *Ann Rheum Dis* 2014;73:396–400.
78. Emery P, Durez P, Dougados M, *et al*. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the adjust trial). *Annals of the Rheumatic Diseases* 2010;69:510–6.

79. Verstappen SMM, McCoy MJ, Roberts C, *et al*. Beneficial effects of a 3-week course of intramuscular glucocorticoid injections in patients with very early inflammatory polyarthritis: results of the STIVEA trial. *Annals of the Rheumatic Diseases* 2010;69:503–9.
80. Machold KP, Landewé R, Smolen JS, *et al*. The stop arthritis very early (save) trial, an international multicentre, randomised, double-blind, placebo-controlled trial on glucocorticoids in very early arthritis. *Annals of the Rheumatic Diseases* 2010;69:495–502.
81. Hilliquin S, Hugues B, Mitrovic S, *et al*. Ability of disease-modifying antirheumatic drugs to prevent or delay rheumatoid arthritis onset: a systematic literature review and meta-analysis. *Ann Rheum Dis* 2018;77:1099–106.
82. van der Helm-van Mil AHM, Zink A. What is rheumatoid arthritis? Considering consequences of changed classification criteria. *Ann Rheum Dis* 2016.
83. Burgers LE, Allaart CF, Huizinga TWJ, *et al*. Brief Report: Clinical Trials Aiming to Prevent Rheumatoid Arthritis Cannot Detect Prevention Without Adequate Risk Stratification: A Trial of Methotrexate Versus Placebo in Undifferentiated Arthritis as an Example. *Arthritis & Rheumatology* 2017;69:926–31.
84. Bos WH, Dijkmans BAC, Boers M, *et al*. Effect of dexamethasone on autoantibody levels and arthritis development in patients with arthralgia: a randomised trial. *Annals of the Rheumatic Diseases* 2010;69:571–4.
85. Stack RJ, Sahni M, Mallen CD, *et al*. Symptom complexes at the earliest phases of rheumatoid arthritis: a synthesis of the qualitative literature. *Arthritis & Rheumatism* 2013;65:1916–26.
86. van der Linden MPM, le Cessie S, Raza K, *et al*. Long-term impact of delay in assessment of patients with early arthritis. *Arthritis & Rheumatism* 2010;62:3537–46.