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Review article

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Rheumatoid arthritis prevention in arthralgia: fantasy or reality?

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Abstract

The concept of a 'window of opportunity' in treating a disease assumes the existence of a time frame during which the trajectory of the disease can be effectively and permanently modified. In rheumatoid arthritis (RA), optimal timing of this period is presumed to be during the phase before arthritis is clinically apparent and disease is diagnosed. Several proof-of-concept trials of treatment during the 'arthralgia' phase of RA have been completed in the past 4 years, with the underlying notion that temporary treatment at this stage could prevent the development of RA or induce a sustained reduction in the burden of disease. This Review summarizes the results of these trials and reflects on the outcomes in relation to the patients' perspectives. Overall, the majority of symptomatic at-risk individuals could benefit from a fixed period treatment, even if RA does not develop. Various factors must be taken into consideration when translating these findings into clinical practice. More evidence is needed to target the individuals at highest risk, and additional tools are needed to monitor treatment and guide decisions about whether treatment can be discontinued. Without these tools, there is a paradoxical risk of seemingly increasing the incidence of the disease and prolonging disease duration, which is the opposite of what the concept of intervening in the window of opportunity entails.

Sections

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Key points

- The therapeutic 'window of opportunity' in rheumatoid arthritis presumes that disease processes are less matured and more modifiable in the symptomatic pre-arthritis phase, fuelling the design of 'prevention trials'.
- Although the populations studied in these trials varied slightly, the at-risk individuals included those with a combination of symptoms (clinically suspect arthralgia), autoantibodies and subclinical inflammation on imaging.
- The first 'proof-of-concept' prevention trials suggest that disease modification could be possible with temporary treatment initiated in an at-risk pre-arthritis phase.
- Nonetheless, treatment in a symptomatic at-risk phase without clinical arthritis is not yet recommended by any treatment guideline.
- Before findings can be implemented, validated tools are needed for risk stratification to guide treatment-start decisions and for monitoring (a 'disease activity score for clinically suspect arthralgia') to guide treatment-withdrawal decisions.

Introduction

Disease outcomes of rheumatoid arthritis (RA) have greatly improved over the past few decades owing to earlier initiation of treatment, treat-to-target treatment strategies and the emergence of novel anti-rheumatic drugs. Nevertheless, the burden of RA, which stands as one of the most prevalent autoimmune diseases[1], is still high and leads to a loss of functional ability and work participation and the long-term use of antirheumatic drugs in the majority of patients[2]. The key to further improving disease outcomes could lie in the timing of DMARD therapy.

A diagnosis of RA requires the presence of clinical arthritis, manifest as swollen joints, but the disease process actually begins many years earlier, with serum autoantibodies emerging up to 10 years before diagnosis[3–5]. Autoantibody responses mature approximately 3 years before disease diagnosis, as evidenced by an increase in autoantibody levels, number of isotypes, antigen specificities and glycosylation of the immunoglobulin fragment antigen-binding (Fab) domain. These features seem to be the critical first steps in the development of autoantibody-positive RA[6–10]. What follows are increases in the expression of various inflammatory factors, such as cytokines and chemokines, estimated to occur about 2 years before diagnosis, but which also occur during the development of anti-citrullinated protein antibody (ACPA)-negative RA[5,6,11]. In high-risk individuals, symptoms occur 6–12 months before diagnosis. At this symptomatic pre-RA stage, individuals at risk visit rheumatology practices and are clinically identifiable. The disease process is thought to be reversible at this time, as only some of these symptomatic patients progress to developing clinical arthritis and RA. These characteristics (identifiability and reversibility) make this at-risk stage of arthralgia ideal for secondary prevention, or interception[12]. Knowing how to identify individuals at-risk of RA before they enter the chronic disease stage has greatly facilitated the design and delivery of the first RA prevention trials. Indeed, several prevention trials have been conducted over the past decade, with the majority of trial results only being reported since 2022. Hence, the present moment is opportune for researchers and clinicians to draw lessons from these recent developments.

In this Review, we discuss the concept of the window of opportunity in the light of disease prevention. We summarize the results of the different prevention trials, evaluate differences and similarities in study design and trial results, and draw conclusions about the efficacy of interventions in the at-risk stage. These results are reflected in light of what is known about the preferences of patients with RA and those at risk. We conclude with considerations of the current results for clinical practice and propose recommendations for what remains to be determined to optimize treatment strategies in the at-risk stage.

The window of opportunity

The therapeutic window of opportunity in RA is a well-established concept that presumes the presence of a period in which the disease processes are susceptible and can be permanently modified (and not only suppressed) with treatment. Observational studies of patients with classified RA have shown that early treatment is associated with improved disease outcomes, and hence the window of opportunity for modifying the severity of the disease course is believed to include at least the early stage of the disease, after RA is diagnosed[13–17]. With regard to modifying disease development, the 'susceptibility period' of the window probably occurs at a pre-RA stage, as chronicity is generally already established at the time of clinical arthritis and diagnosis of RA. However, observational studies can be subject to confounding factors, and so formal evidence on whether or not early treatment in either RA or at an at-risk stage can permanently modify the disease course should be derived from randomized clinical trials comparing early initiation of DMARD therapy and delayed (placebo) initiation of treatment.

But what is the evidence from randomized controlled trials of the existence and timing of a window of opportunity? Within classified RA, the results from clinical trials have been reviewed elsewhere[18]. Overall, the data have consistently shown that patients with RA who begin DMARD therapy early have better long-term outcomes with less severe radiographic joint damage and better functional ability than patients who have a delayed initiation of DMARD therapy. These trials were performed in the period from 1990 to the early 2000s and early treatment was defined as treatment beginning within 2 years after RA diagnosis[19–22]. Placebo-controlled clinical trials in RA that define early treatment as treatment beginning within 12 weeks of diagnosis have yet to be performed. Nonetheless, within classified RA, early treatment results in sustained disease modification as assessed by improvements in physical functioning and joint damage, and hence not only suppresses the disease but also changes the disease trajectory, as reviewed elsewhere[18].

This approach has been expanded through interventions in pre-RA stages, with the aim of halting the underlying biological processes and consequently preventing the onset of RA. In the period 2000–2010, trials were conducted in patients with undifferentiated arthritis and evaluated the most commonly used DMARDs[23–25]. None of these interventions truly prevented RA development. Therefore, no formal evidence is currently available to support the notion of disease modification at the stage of undifferentiated arthritis. Over the past decade, the field of RA has moved 'forward', to intervening at even earlier stages of disease, with the hypothesis that disease processes are less mature before the onset of clinical arthritis and are therefore more modifiable. Several prevention trials have been performed that could be considered as 'proof-of-concept trials' for evaluating whether interventions at the at-risk stage without the presence of clinical arthritis do indeed induce

disease modification. In the next section of this Review, we discuss the results from these trials to determine if disease modification can be achieved.

In our discussions of these trials, we use the definition of disease modification as outlined by the European Alliance of Associations for Rheumatology (EULAR): "disease modification is a combination of relief of signs and symptoms; improvement or normalization of physical function, quality of life and social and work capacity, and the inhibition of occurrence or progression of structural damage to cartilage and bone"[26]. Although structural damage is rare prior to the presence of clinical arthritis, we can still evaluate the efficacy of interventions in at-risk individuals by considering the sustained effects on signs (clinical arthritis), symptoms, physical function, quality of life and work capacity. Hence, the outcomes considered encompass not only the prevention of clinical arthritis and RA, but also, from a broader perspective, the burden experienced by those at risk. We also incorporate the factor of sustainability into this EULAR definition, meaning that disease modification requires a persistent difference between the intervention and placebo arms, even after treatment discontinuation. Such a requirement makes it possible to distinguish 'real' disease modification from disease suppression. Because the development of RA can take a long time and the suppressive effects of therapy can continue for some time after treatment withdrawal, adequate follow-up is needed in these trials to verify whether the effects are persistent. Figure 1 illustrates the conceptual differences between disease suppression and prevention. Disease prevention can be either prevention of the phase of clinical arthritis and/or RA or prevention of a more severe disease course.

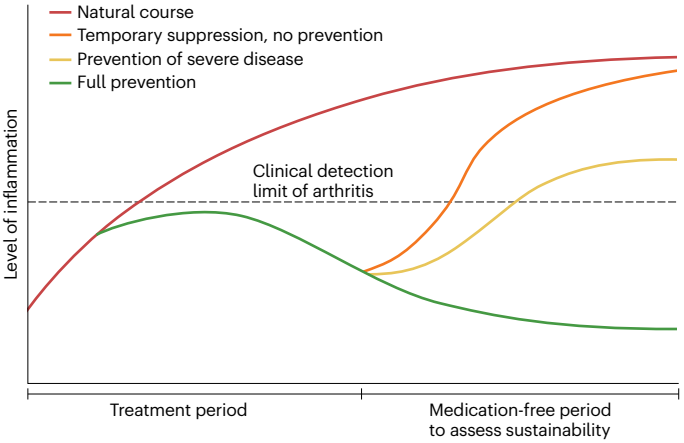

Fig. 1 | Conceptual difference between disease suppression and prevention. Without treatment during the at-risk phase of arthralgia, rheumatoid arthritis (RA) develops following its natural course, involving accumulating levels of inflammation and clinically apparent arthritis (red line). Temporary treatment during the at-risk phase of arthralgia could lead to full prevention of disease (green line), prevention of severe disease (yellow line; that is, the disease course is milder than expected without treatment at the start of this early phase), or temporary suppression of disease but not prevention (orange line; that is, RA ultimately develops with a similar disease course to that without treatment during the pre-arthritis phase).

Proof-of-concept trials in arthralgia

Seven proof-of-concept trials during the at-risk phase have thus far been initiated[27–33] (Table 1). Four of these trials have been completed (Bos et al.[27], 'TREAT Early Arthralgia to Reverse or Limit Impending Exacerbation to RA' (TREAT EARLIER)[29], 'Abatacept Reversing subclinical Inflammation as measured by MRI in ACPA-positive Arthralgia' (ARIAA)[30] and 'Arthritis Prevention In the Preclinical phase of RA with Abatacept' (APIPPRA)[32]), one of the trials stopped when 90% of the planned patient population was reached ('Prevention of clinically manifest RA by B cell directed therapy in the earliest phase of the disease' (PRAIRI)[28] and two of the trials were stopped prematurely because of insufficient enrolment or after interim analyses ('STAtins to Prevent RA' (STAPRA) and 'Strategy to prevent the onset of clinically-apparent RA' (StopRA)[31]). The results of four trials have been reported in full publications[27–29,33] whereas the full publications from the other trials are awaited[30–32]. In the absence of full reports, we used data provided by abstracts. Although detailed information is lacking, the abstracts provide the key findings of the trials and we considered it relevant to include them[30–32]. Although the interpretation of trials that were closed when the inclusion number was not reached and/or the follow-up was not completed is formally limited owing to insufficient power, we have included these trials for completeness. To properly interpret the findings, we will first consider the design of the different trials with regard to the populations of individuals at-risk, interventions and endpoints.

Individuals at risk included in prevention trials

All seven of the prevention trials included individuals with arthralgia (Table 1). Fulfilment of the EULAR definition of arthralgia suspicious for progression to RA was not required because the trials were designed before this definition was published in 2016 (ref. 34). The at-risk individuals were identified in secondary or primary care settings. The StopRA trial was different from the other trials in that individuals without symptoms were also eligible to enrol and participants with autoantibodies identified in the general population were also included. In this trial, 63% of participants were identified at rheumatology practices and 37% were asymptomatic.[31] The definition of the symptoms varied between the trials. Patients included in the TREAT EARLIER trial had clinically suspect arthralgia (CSA), a term used to define a complex of clinical symptoms and signs in patients at risk of progression to RA on the basis of clinical expertise of the rheumatologist[29,35]. By contrast, in the other trials, the joint symptoms were not further specified as inclusion requirements. In addition to the presence of symptoms, the inclusion criteria for some of the trials included positivity for various laboratory and/or imaging criteria. The trials by Bos et al.[27], PRAIRI[28], ARIAA[30], APIPPRA[32], STAPRA[33] and StopRA[31] required the presence of autoantibodies (positivity for ACPAs and/or rheumatoid factor). By contrast, the TREAT EARLIER trial[29], the largest prevention trial to date, did not have this inclusion criterion and could therefore also evaluate the efficacy of intervening in a pre-arthritis phase of autoantibody-negative disease. To include patients with sufficient risk of RA, in addition to the requirement of having CSA, the presence of subclinical joint inflammation on MRI of the hand and foot was needed for inclusion. MRI inflammation was assessed by the RA-MRI scoring system, a validated scoring system for MRI inflammation in RA that evaluates osteitis, synovitis and tenosynovitis[36,37]. In the TREAT EARLIER trial[29], subclinical joint inflammation was strictly defined by the presence of inflammation (osteitis, synovitis and/or tenosynovitis) in at least one joint that is present in less than 5% of an age-matched symptom-free population at the same location[29,38]. The ARIAA trial also required the presence of subclinical joint inflammation for inclusion[30]. However, in this trial, subclinical joint inflammation was defined as the presence of any synovitis,

Table 1 | Proof-of-concept prevention trials in patients with arthralgia

Ref.	Status	Participants (n)	Intervention	Outcome
Bos et al.[27]	Completed (full publication available)	Individuals with arthralgia, positive for ACPAs and/or RF and positive for a shared epitope allele (*n*=83)	Dexamethasone (100 mg intramuscular injection) or placebo, twice	Primary: 50% reduction of ACPAs and/or RF levels at 6 months. Secondary: clinical arthritis
PRAIRI[28]	Completed (full publication available)	Individuals with arthralgia, positive for ACPAs and RF, and with hsCRP ≥0.6 mg/l (*n*=81; target number 90)	Rituximab (1,000 mg intravenous injection) or placebo (NaCl 0.9%), combined with methylprednisolone (100 mg intravenous injection), once	Clinical arthritis
TREAT EARLIER[29]	Completed (full publication available)	Individuals with clinically suspect arthralgia and subclinical inflammation on MRI of most painful or dominant hand or foot (defined as synovitis, tenosynovitis or osteitis in ≥1 joint that is present in <5% of age-matched symptom-free controls at the same location) (*n*=236)	Methotrexate (25 mg/week) for 12 months combined with one injection methylprednisolone (120 mg intramuscular) at baseline, or placebo for 12 months	Primary outcome: clinical arthritis that persisted ≥2 weeks (RA according to the ACR–EULAR 2010 criteria or involving ≥2 joints); secondary outcomes: physical functioning, symptoms, work productivity and course of MRI inflammation
ARIAA[30]	Completed (abstract available only)	Individuals with arthralgia, positive for ACPAs and with evidence of subclinical inflammation on MRI of the dominant hand (defined as any synovitis, tenosynovitis or osteitis) (*n*=98)	Abatacept (125 mg subcutaneous injection weekly) or placebo for 6 months	Primary: improvement of MRI-inflammation. Secondary: RA development
APIPPRA[32]	Completed (abstract available only)	Individuals with arthralgia who are positive for both ACPAs and RF or who have high serum levels of ACPAs (*n*=213)	Abatacept (125 mg subcutaneous injection weekly) or placebo for 12 months	Clinical arthritis in three or more joints or RA according to the ACR–EULAR 2010 criteria
STAPRA[33]	Prematurely stopped owing to low inclusion rate and treatment adherence (full publication available)	Individuals with arthralgia who are positive for both ACPAs and RF or who have high serum levels of ACPAs (*n*=62; target number 220)	Atorvastatin (40 mg daily) or placebo for 3 years	Primary outcome: clinical arthritis; secondary outcome: RA according to the ACR–EULAR 2010 criteria
StopRA[31]	Prematurely stopped owing to futility during interim results (abstract available only)	Individuals with or without arthralgia who are positive for ACPAs (*n*=142; target number 200)	Hydroxychloroquine (200–400 mg daily) or placebo for 1 year	RA (fulfilling criteria of inflammatory arthritis and ≥1 erosion on radiography)

ACPA, anti-citrullinated peptide antibodies; hsCRP, high-sensitivity C-reactive protein; RA, rheumatoid arthritis; RF, rheumatoid factor.

tenosynovitis or osteitis on MRI of the dominant hand, according to the RA-MRI scoring system. This definition of subclinical joint inflammation did not use a reference of MRI findings in asymptomatic individuals who are known to be present in the general population, especially at increasing age[30,38]. The other trials did not require subclinical joint inflammation to be present at the time of inclusion.

Overall, the populations included in the different prevention trials differed to some extent. This variation is reflected by the differences in average risk of RA development observed in the different trials, which ranged from 7 to >50% in the placebo arms of the trials during the follow-up periods (Table 2). The patient characteristics also differed amongst the studies (Table 2). For example, in the TREAT EARLIER trial[29], in which the presence of the CSA phenotype was required, the frequency of morning stiffness ≥60 min was 35%, with a median tender joint count (TJC-68) of 3. By contrast, for some other trials in which the presence of autoantibodies was an important criterion, morning stiffness was less frequent and median tender joint count lower; for instance, in the Bos et al.[27] and PRAIRI trials[28], morning stiffness ≥60 min was infrequent (7%) and median TJC (TJC-44) was 0. Nevertheless, despite some differences in patient characteristics and perceived risks of RA, the majority of studies included patients with joint symptoms combined with additional risk factors, either the presence of subclinical joint inflammation and/or autoantibody positivity.

Drugs studied in prevention trials

The processes that drive progression from (clinically suspect) arthralgia to RA or that are involved in resolution of the at-risk stages of CSA and/or subclinical joint inflammation are unclear. Nevertheless, the trial hypothesis was that earlier treatment initiation would be sufficient to sustain benefit over the longer term. In the absence of evidence-based knowledge on which processes to target, the trials examined both conventional and biological DMARDs commonly used in established RA to suppress disease activity[39] (Table 1): methotrexate (TREAT EARLIER[29]) and steroids (Bos et al.[27]), which are cornerstone (first-step) treatments in RA, hydroxychloroquine (StopRA[31]), the DMARD with the most favourable safety profile, as well as the B cell-depleting therapy rituximab (PRAIRI[28]) and the co-stimulatory blocker abatacept (ARIAA[30] and APIPPRA[32]), which are thorough in modulating the early stages of inflammation by blocking the interaction between T cells and antigen-presenting cells. Cytokine blockers such as TNF inhibitors have not yet been studied in prevention trials because of the underlying assumption that immune modulation is more effective than cytokine blockade at such an early stage of disease that

has minimal or modest inflammatory burden. The effect of this group of DMARDs at the at-risk stage is thus still undetermined. Atorvastatin (STAPRA[33]), a lipid-lowering drug that is not known for its efficacy in RA, was studied, as this drug has an anti-inflammatory effect, including in animal models, and is associated with a decreased risk of RA development in large population studies. A multidisciplinary lifestyle programme that improves outcomes in other chronic diseases was also studied in the Plants for Joints trial[40].

The dosing schedules used for the DMARDs were largely influenced by licensed dosing regimens. Single doses and prolonged, fixed periods of treatment periods were included (Table 1). The Bos et al.[27] trial studied the efficacy of two intramuscular injections of corticosteroids, whereas the PRAIRI trial assessed the effects of a single infusion of rituximab.[28] In the other trials, individuals were treated during a longer period: the TREAT EARLIER trial involved a single injection of intramuscular corticosteroids combined with a 1-year course of methotrexate, the ARIAA trial involved a 6-month treatment with abatacept, the APIPPRA involved treatment with abatacept over 1 year and the StopRA trial involved 1-year treatment with hydroxychloroquine[29–32]. The STAPRA trial planned a 3-year treatment period with atorvastatin[33]. In general, a wide variety of commonly used antirheumatic drugs have been studied for disease modification at the stage of arthralgia.

Endpoints evaluated in prevention trials

All trials evaluated the development of clinical arthritis as an outcome (Table 1), with most studies having clinical arthritis as a primary end point. Some trials had additional requirements to the presence of clinical arthritis, for instance, that clinical arthritis had to be persistent for at least 2 weeks in two or more joints[29], fulfilled American College of Rheumatology (ACR)–EULAR 2010 classification criteria for RA[29–31,41] or was accompanied by an erosion on radiography[31]. The period after treatment cessation during which endpoints continued to be collected (relevant to estimate sustainability of an effect) varied slightly, but was most commonly at least 1 year (Table 1). Other endpoints were assessed related to the disease burden,[29,32] symptom complexes, levels of subclinical joint inflammation[29,30] and levels of autoantibodies[27,28]. In general, the endpoints reflected the development of RA itself or risk factors for the development of RA.

Efficacy of interventions in autoantibody-positive arthralgia

In this section, we discuss the efficacy of treatment in autoantibody-positive at-risk individuals (as opposed to autoantibody-negative individuals), whereby prevention concerns the prevention of autoantibody-positive RA development (Table 3). Two injections of corticosteroids and a 1-year course of hydroxychloroquine could not prevent progression to autoantibody-positive RA in the Bos et al. and StopRA trials[27,31]. Furthermore, rituximab therapy (in the PRAIRI trial) or a 1-year course of methotrexate (in a subgroup analysis of ACPA-positive individuals in the TREAT EARLIER trial) could not prevent the development of autoantibody-positive RA, as assessed by the two year endpoints[28,29]. Despite the absence of RA prevention in these trials, the results of both trials suggested that either intervention delayed RA development as the patients less frequently progressed to clinical arthritis during the treatment phase than those individuals in the placebo group. Abatacept is the only intervention studied to date that seemed to reduce the development of RA at the end of the follow-up period. In the ARIAA trial, after 18 months, 35% of patients developed RA in the abatacept treatment arm versus 57% in the placebo arm[30]. In the APIPPRA trial, at the end of the study at 24 months (that is, 12 months after stopping the trial medication), 37% of participants progressed to RA in the placebo arm versus 25% in the abatacept arm[32]. In both trials of abatacept, the differences in RA development between the intervention and placebo groups were larger during the treatment period than during the subsequent treatment-free period, indicating a reduced treatment effect over the second year. Note that the difference in percentage of individuals who progressed to developing RA

Table 2 | Patient baseline characteristics of prevention trials in arthralgia

Baseline characteristic	Bos et al.[27]	PRAIRI[28]	TREAT EARLIER[29]	ARIAA[30a]	APIPPRA[32a]	STAPRA[33a]	StopRA[31a]
Prior risk of clinical arthritis development[b]	20%	40%	18%	NR	NR	19%	NR
Prior risk of RA development according to 2010 criteria[b]	7%	28%	14%	57%	37%	19%	36%
Age (mean)	48 years	53 years	47 years	49 years	49 years	46 years	49 years
Female	66%	60%	68%	80%	77%	81%	80%
First-degree relative with RA	NR	NR	27%	NR	NR	NR	8%
Symptom duration (median)	52 weeks	NR	27 weeks	NR	NR	NR	NR
Morning stiffness ≥60 min	7%	NR	35%	NR	NR	NR	NR
VAS pain (0–100 scale)	20 (median)	NR	50 (median)	43 (mean)	24 (mean)	NR	NR
Tender joint count[c]	0 (median)	0 (median)	3 (median)	3.5 (mean)	5 (mean)	1 (median)	NR
C-reactive protein (median)	2.4 mg/l	2.9 mg/l	3 mg/l	NR	4 mg/l	2 mg/l	NR
Rheumatoid factor-positive	68%	98%	32%	NR	86%	55%	NR
ACPA-positive	71%	100%	20%	100%	100%	100%	100%

Presented are the baseline characteristics of the placebo arm, the characteristics of the treatment arm are similar, as expected by randomization. Note that means and medians cannot be compared because of possible skewed data by outliers. ACPA, anti-citrullinated peptide antibody; NR, not reported; RA rheumatoid arthritis; VAS, visual analogue scale. [a]Abstract publication (full article not yet published). [b]Defined as risk of development over the follow-up period in the placebo group. [c]Tender joint count (TJC)-44 for Bos et al.[27], TJC-68 for PRAIRI[28], TREAT EARLIER[29], ARIAA[30] and APIPPRA[32].

Table 3 | Observed efficacy of interventions on disease modification in prevention trials

Study	Intervention	Treatment period	Follow-up period after treatment	Effect on progression to RA	Effect on subclinical inflammation	Effect on symptoms and function
Autoantibody-positive at-risk individuals						
Bos et al.[27]	Dexamethasone (100 mg intramuscular injection)	Two injections at 0 and 6 weeks	26 months (median)	No effect	–	–
PRAIRI[28]	Rituximab (1,000 mg intravenous infusion)	Single infusion at baseline	29 months (median)	No effect (possible delay)	–	–
TREAT EARLIER[29]	Methotrexate (25 mg/week) combined with methylprednisolone (120 mg intramuscular injection) at baseline	12 months	12 months	No effect	Improvement in MRI-inflammation (sustained at 24 months)	Improvement in symptoms, functional ability and work ability (sustained at 24 months)
ARIAA[30]	Abatacept (125 mg subcutaneous injection weekly)	6 months	12 months	Lower progression (35% with treatment versus 57% with placebo) at 18 months	Improvement in MRI-inflammation at 6 months (sustainability at 18 months not yet known)	–
APIPPRA[32]	Abatacept (125 mg subcutaneous injection weekly)	12 months	12 months	Lower progression (25% with treatment versus 37% with placebo) at 24 months	–	–
StopRA[31]	Hydroxychloroquine (200–400 mg daily)	12 months	Planned 36 months (stopped prematurely)	No effect	–	–
Autoantibody-negative at-risk individuals						
TREAT EARLIER[29]	Methotrexate (25 mg/week) combined with methylprednisolone (120 mg intramuscular injection) at baseline	12 months	12 months	No effect	Improvement in MRI-inflammation (sustained at 24 months)	Improvement in symptoms, functional ability and work ability (sustained at 24 months)

in the placebo arms of the ARIAA and APIPPRA trials (57% and 37%, respectively) likely reflect the requirement for inclusion of MRI inflammation in the dominant hand of the study participants in the ARIAA trial (thus, selecting participants with a higher risk than those selected in the APIPPRA trial). Nonetheless, the fold change in progression rates between the placebo and treatment arms was similar in both trials of abatacept. In the Plants for Joints trial[42], a multidisciplinary lifestyle programme did not seem to result in any notable improvements in terms of RA development. However, this trial was optimized for assessing the effects of this programme on patients with classified diseases (RA and osteoarthritis) and did not have sufficient power to effectively assess the effect on the arthralgia subgroup, encompassing a total of 17 individuals.

Disease burden has so far only been studied as a key end point in one trial (the TREAT EARLIER trial)[29]. In this trial, the ACPA-positive at-risk individuals who received methotrexate had sustained improvements in physical functioning, symptoms such as pain and presenteeism at work. These improvements persisted in the year after cessation of treatment. In a post hoc analysis, improvements in outcomes used to measure disease burden were noted in both individuals who developed RA and individuals who did not develop RA. Thus, pivotal measures of the disease burden (such as functional ability and symptoms) were less severe at the time of diagnosis in those that developed RA but were also persistently improved in individuals who did not develop RA. Interestingly, this finding implies that the majority of at-risk individuals could benefit from temporary treatment in the CSA phase, irrespective of whether they develop RA. In addition, in the APIPPRA trial, the ACPA-positive at-risk individuals who received abatacept had lower tender joint counts, pain and HAQ scores during the treatment period than those individuals in the placebo group[32]. Although more detailed results are not yet available for the APIPPRA trial, these findings are in line with the reduced disease burden observed in the intervention group of the TREAT EARLIER trial[29].

Both the TREAT EARLIER and ARIAA trials assessed the course of subclinical joint inflammation (as detected by MRI) following treatment[29,30]. Both methotrexate and abatacept therapy resulted in a decreased level of subclinical joint inflammation at the end of the treatment period. Methotrexate treatment also provided sustained reductions in subclinical joint inflammation at 24 months (12 months after treatment cessation)[29]. The ARIAA trial also assessed the effect of abatacept on subclinical joint inflammation at 18 months, but the results have not yet been released. Notably, functional disability and inflammatory symptoms such as joint pain and morning stiffness are related to the presence of subclinical joint inflammation[43–45]; the findings that both symptoms and subclinical joint inflammation improve with treatment therefore support the validity of the results.

Two of the trials assessed the effect of treatment on autoantibody levels (Bos et al.[27,28] and the PRAIRI trial[26]). Intramuscular corticosteroid

therapy did not reduce levels of ACPAs and/or rheumatoid factor by at least 50% (a predefined end point), but median levels of ACPAs were slightly lower after 6 months (−8% in the treatment group versus +3% in the placebo group when compared with the baseline ACPA level); data at the study end (median 26 months) were not provided[27]. By contrast, rituximab therapy did not result in any decrease in ACPA level[28].

Efficacy of interventions in ACPA-negative arthralgia

The efficacy of preventive interventions in autoantibody-negative disease was only assessed in one trial (TREAT EARLIER)[29] (Table 3). Intriguingly, the results were mostly similar to those seen in patients with autoantibody-positive RA. Methotrexate did not prevent the development of autoantibody-negative RA. However, treatment did result in sustained improvements in the disease burden (pain, morning stiffness, physical functioning and presenteeism) and the extent of subclinical joint inflammation.

Overall efficacy of interventions in arthralgia

In light of the EULAR definition of disease modification, the results of currently available 'proof-of-concept' prevention trials suggest that disease modification is possible with a temporary fixed-period treatment when initiated in an at-risk pre-arthritis phase (Table 3). Furthermore, sustained reductions in disease burden and subclinical inflammation are possible with such interventions. Importantly, the effects can persist even after treatment withdrawal, indicating that not only is the disease burden temporarily suppressed with treatment but that the treatment has sustained effects on disease development. These data provide the first proof of disease modification in a 'pre-RA' phase. Whether disease development can be fully prevented is less evident. The majority of conventional and biologic DMARDs studied did not show a sustained preventive effect on RA development, with the exception of abatacept. Both trials of abatacept showed a difference between placebo and abatacept treatment during the treatment period that diminished somewhat after treatment cessation but still persisted up to the last study visit. Data from longer follow-up will be interesting, to fully differentiate permanent prevention from suppression.

What else can be expected from current prevention trials?

In the preceding sections, we have described the first results of the prevention trials; however, further information could be gleamed from these trials in the future. First, some of the trials have so far only been released in abstract form, and the full publications of the trial results could reveal additional information to that extracted here[30–32]. In addition, the APIPPRA and TREAT EARLIER, among others, have extended their observation period for up to 5 years[46,47], which could reveal interesting insight in the future. For example, such long-term data will be important to evaluate the sustainability of the preventive effects (including showing whether an intervention simply delays or prevents disease), both with respect to RA development and reducing the severity of the disease burden of at-risk individuals. Additionally, a longer follow-up period for the participants who developed RA will show whether a temporary treatment in the pre-arthritis phase results in a milder disease course ('prevention of severe RA', as illustrated in Fig. 1) and/or a higher chance of achieving DMARD-free remission.

Considerations of patient preferences

Gaining insight into how at-risk individuals perceive the idea of initiating early treatment during the symptomatic phase, in the absence of a disease diagnosis, is important. This understanding not only aids in effective implementation of the trial results but also helps in the design of future trials. Several qualitative and quantitative studies have been performed in at-risk individuals and/or first-degree relatives of patients with RA to assess their preferences, for example, through the use of hypothetical scenarios[48–54]. These studies have confirmed irrefutably that a proportion of individuals at risk of RA are willing to take preventive treatment. Additionally, individuals with symptoms were more willing to take preventive medication than those without symptoms[48,49]. The predicted uptake of preventive medication is higher for oral medication than for drugs administered via injections and is also higher for non-biologic drugs than for biologic drugs[50,51], although some individuals prefer intravenous treatment[53]. Quantitative studies have also shown that willingness depends on the assumed risk of RA development: 7%, 30% and 38% of at-risk individuals were willing to take medication when the assumed risk of RA was 1%, 20% and 40%, respectively[52]. In addition, willingness depends on treatment efficacy; for example, in one study, willingness was highest if treatment was predicted to decrease the risk of developing RA in 5 years from 60% to 24%, whereas the willingness decreased if the predicted risk reduction was lower (that is, reducing the risk from 60% to 34% or 44%)[51]. The perceived extent of RA risk reduction was also associated with tolerance to some of the risks associated with preventive treatment (such as risk of infection)[54].

Comparing the percentage of individuals who were willing to take preventive medication in these quantitative studies with the observed percentages of individuals who actually accepted preventive interventions with DMARDs in the prevention trials could also provide useful insight. The prior risk of RA in these trials ranged between 7% and 57% (Table 2). The numbers of participants screened and the reasons for consent are not (yet) available for most trials. However, one trial has reported that 23% of the eligible patients (89 out of 384 eligible participants) did not wish to participate in the trial; being unwilling to take DMARDs might be one of the reasons for not participating[29]. These data suggest that the uptake rate is actually higher when at-risk individuals are presented with a real proposition of a DMARD than the rates observed in hypothetical scenarios in qualitative studies. On the contrary, difficulty with inclusions in some other trials might be partly caused by unwillingness of at-risk individuals to accept DMARD therapy[31,33]. The view of patients on preventive medications and reasons for adopting preventive medication therefore remains an important subject for research. Moreover, all studies on this matter have so far focused on full prevention of RA. Studies on willingness to accept preventive interventions to reduce the severity of disease burden have not yet been published.

Current gaps and limitations

Two crucial gaps in our knowledge remain that might hamper the achievement of the full prevention of RA. The first is that the 'point of no return' in developing disease chronicity is still unknown. Chronicity is usually established at the time of clinical arthritis and diagnosis of RA. However, the precise point in the pre-arthritis period at which the process of chronification concludes and disease chronicity becomes fully established remains unclear. The observation that only a proportion of patients with autoantibody-positive arthralgia or CSA progress to RA and that part of these at-risk individuals even experience resolution of symptoms and subclinical joint inflammation[35,55–57] implies that chronicity has not yet been established at the time of symptom onset. However, the (sub)stages in the trajectory from CSA to RA, and the 'point of no return', have not yet been identified. Thorough serial studies are needed

to map this trajectory in detail, to determine when the disease processes are modifiable to such an extent that the disease can be fully prevented, and to determine when this susceptible period 'closes' and the 'point of no return' has passed. This precise point should be determined for both autoantibody-positive and autoantibody-negative disease, as the timing of the point of no return in both disease subsets could differ.

In light of this concept, some insight can be gained from a pre-specified sub-analysis of the TREAT EARLIER trial[29], which analysed a subset of patients at a high risk of RA development (>70%). These patients had CSA, autoantibodies and extensive subclinical joint inflammation. The combination of these features might indicate that the disease in these patients was fairly advanced in its trajectory towards RA. Intervention in this group delayed but did not prevent disease, as after treatment discontinuation the difference between the treatment and placebo arms disappeared. One possible explanation could be that the disease in these high-risk patients was already well advanced in its trajectory from CSA to RA and had already passed the point of no return. If this explanation were true, prevention could still be possible for patients when treated in the earlier sub-stages of disease. Thus, the ability to substage the trajectory from CSA to RA and to define a 'point of no return' for developing chronic disease would allow the design of subsequent prevention trials that include patients 'at the right time' of disease.

The second gap in our knowledge relates to understanding the critical mechanism(s) involved in turning subclinical joint inflammation into irreversible clinical arthritis and RA, as well as those mechanisms involved in the resolution of subclinical joint inflammation. Understanding these processes is crucial for identifying which specific pathways to target with therapeutic interventions. So far, the drugs studied are known for their effectiveness in suppressing disease activity in RA. The mechanisms critical in the eventual development of RA might differ from those mechanisms involved during established disease and the suitable preventative treatments could therefore differ from the therapeutic arsenal currently available. Examination of the maturation of autoantibody responses has revealed that they remain unchanged during progression from CSA to RA and are not different in individuals with CSA who develop RA from those individuals with CSA who do not[58,59]. This finding suggests that various antibody characteristics (such as the autoantibody level, number of isotopes and Fab-glycosylation) are unrelated to the 'final hit' that triggers progression from CSA to RA. Other features must therefore trigger the development of full disease, such as the interplay between inflammatory and inhibitory ACPAs (as described in mouse models[60]) or factors other than autoantibodies. Cytokine expression in the systemic circulation also remains stable during the progression from CSA to RA[61]. Such investigations were performed using blood samples, whereas studying the joint tissue might also help to elucidate the final processes that determine the development of RA. For example, differences in specific cell subsets or transcription factors could be crucial in the mechanisms that drive progression from the at-risk symptomatic phase to RA, which could be specifically targeted. Another approach to consider in early disease intervention is the induction of tolerance through targeting inhibitory checkpoints (such as PD1 agonism) or antigen-specific tolerizing immunotherapy[62,63]. As conducting prevention trials is extremely labour intensive and expensive, the choice of intervention in future trials should be based on pathophysiological knowledge gained from basic research. Ultimately, future trials should aim to intervene with the 'right intervention at the right time'.

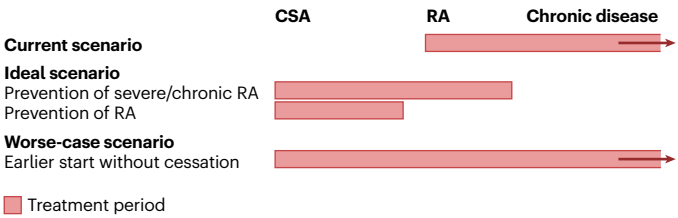

Fig. 2 | Duration of DMARD treatment for rheumatoid arthritis: current, ideal and worst-case scenarios. Currently, DMARD treatment is initiated when a patient is diagnosed with early rheumatoid arthritis (RA), in line with current guidelines (current scenario). Ideally, DMARD therapy would be started in the pre-arthritis phase and reduce the length or severity of RA or fully prevent RA development (ideal scenario). However, DMARD treatment initiation in the pre-arthritis phase could also result in a scenario in which the disease or treatment duration is prolonged (rather than shortened), as DMARD treatment is initiated early and not tapered or stopped (worst-case scenario). CSA, clinically suspect arthralgia.

Implementation in clinical practice

Before trial results can be applied to clinical practice, several important aspects must be considered, as discussed in this next section.

Which patients?

At-risk individuals generally want to be informed of their risk of developing RA and/or the current (sub)stage of their disease in transitioning to RA. Although several cohorts have published prediction models[35,56,57], none of the prediction models has yet been validated in independent cohorts. In 2021, the EULAR taskforce summarized core sets of risk factors for clinical arthritis in different at-risk populations, which included clinical features, antibody profiles, genetic markers, serum and cellular markers and subclinical inflammation on imaging[64,65]. However, no consensus has yet been reached on a risk stratification method that is feasible for the field. To address this gap, an ongoing EULAR–ACR taskforce that includes experts from more than ten European countries and the USA has joined forces to combine and analyse the data of symptomatic at-risk individuals from ten different cohorts, with the aim of developing validated risk stratification criteria[66]. The primary purpose of this task force is to support the design of future prevention studies, but the results might be considered useful in clinical practice.

So far, RA prevention trials have only intervened in the symptomatic at-risk stage, but intervention could be even more effective at an earlier stage when systemic autoimmune responses are still developing and maturing. However, most individuals at this earlier stage of disease are asymptomatic, posing difficulties for risk stratification. This difficulty might explain why no trials of at-risk populations involving only asymptomatic individuals have yet been performed.

Which type of intervention?

Importantly, treating patients with arthralgia without clinical arthritis is against EULAR recommendations[39,67] and therefore cannot yet be advocated. If treatment were to be considered or recommended in the future, which intervention should be used? The currently available data (discussed earlier in the Review) do not support the use of hydroxychloroquine or intramuscular injections of corticosteroids (as a single therapy) for RA prevention[27,31]. Methotrexate might be considered for the purpose of improving physical functioning or the reduction of symptoms, the outcomes of which are presumably mediated by lowering levels of (subclinical) inflammation[29]. Biologic DMARDs are

Box 1

Research agenda

Current proof-of-concept prevention trials:

- Publication of the full results of the 'Abatacept Reversing subclinical Inflammation as measured by MRI in ACPA-positive Arthralgia' (ARIAA) and 'Arthritis Prevention In the Preclinical phase of RA with Abatacept' (APIPPRA) trials, to improve the comparability of the findings from the different trials.
- Publication of the longer follow-up data of the trials with abatacept and methotrexate, to determine the sustainability of the observed effects (that is, to determine the sustainability of rheumatoid arthritis (RA) prevention with abatacept and the sustainability of the reduction in disease burden with methotrexate).
- For methotrexate and abatacept: to determine the optimal treatment duration in the symptomatic at-risk phase.

Future steps:

- To establish a highly accurate risk stratification system to facilitate the design of future prevention trials, which should help in the selection of individuals who will likely benefit from treatment (high prior risk) rather than individuals who will not (low prior risk) to prevent overtreatment.
- To develop a validated disease activity score to monitor effectiveness of early intervention before reaching the end point of RA (a 'disease activity score' for clinically suspect arthralgia).
- To achieve targeted treatment by unravelling the molecular mechanisms promoting progression from arthralgia to RA.
- To determine whether the mechanisms that result in disease chronicity are similar for autoantibody-positive and antibody-negative RA.
- To determine the willingness of individuals who are actually at risk of progression to RA to accept treatment at the at-risk stage with the goal of resolving symptoms or reducing disease severity (rather than preventing the development of RA).
- To determine the societal benefit and cost-effectiveness of treatment in the at-risk phase.
- To determine if and which lifestyle interventions can modify the disease course in the symptomatic at-risk phase of RA.
- To determine the efficacy of different DMARDs for the prevention of RA when applied in the asymptomatic at-risk stage.

now formally limited to treating the disease stage of RA, for patients in whom treatment with (more than one) conventional DMARDs has failed[39]. Using biologic DMARDs as first-line therapy in arthralgia is far from the current recommendations and will be difficult to support, as long as the rules (including rules surrounding reimbursement by health care insurance) remain unchanged.

Providing lifestyle recommendations is tempting, as such interventions are generally valuable for promoting health and well-being. Whether cessation of smoking or lowering weight is useful at the stage of CSA is unclear. Data from observational studies suggest that smoking and obesity are associated with the onset and broadening of the autoimmune response during the asymptomatic period. But once autoimmune responses are established, data from several arthralgia cohorts suggest that smoking and obesity do not increase the risk of developing RA in CSA[68,69]. Hence, these observational data do not support the idea of weight reduction and smoking cessation for reducing the likelihood of RA development in individuals already at the at-risk stage of CSA. The results of the Plants for Joints trial showed no benefit for a range of lifestyle interventions in autoantibody-positive arthralgia, but the sample size was small (17 individuals)[40]. Further research on non-pharmacological approaches is needed to gain evidence of the effect of lifestyle interventions such as risk education, weight loss, smoking cessation or periodontal treatment in the symptomatic at-risk phase[70].

How to monitor the efficacy of preventive treatment?

A pivotal issue in preventive treatment is effectively monitoring treatment efficacy at the stage of arthralgia. The currently performed trials used RA development as an efficacy end point. By definition, this approach requires a long-term follow-up period before conclusions can be drawn about treatment efficacy. A monitoring system is needed that is tailored to the at-risk stage of the disease. For example, in the management of cardiovascular risk, patients are often treated with antihypertensive drugs or statins to prevent cardiovascular events, but the efficacy of such preventive strategies is not assessed by measuring cardiovascular events, but by measuring changes in blood pressure or cholesterol levels. Similarly, a rapid evaluation of response to treatment in CSA is required. The commonly used disease activity score (DAS) is not designed for the at-risk setting in which the pivotal component 'number of swollen joints' is per definition zero[71]. Using the DAS in arthralgia would imply that treatment is then mostly guided by pain. Assuming that measuring a treatment response in CSA is valuable, it is fully justifiable to invest future time and effort in developing a DAS that is specific to the stage of CSA. Such a DAS might be a multidimensional score that includes patient-reported symptoms, information on physical examination (for example, joint tenderness) and serological and functional assessments such as grip strength[44]. Future studies are required to develop and validate a DAS for the at-risk stage of CSA.

How to minimize the risk of overtreatment?

Overtreatment is intrinsic to preventive treatments. For instance, with respect to the use of statins, most patients taking statins will never experience a cardiovascular event, although long-term statin treatment is recommended for individuals with a 10% risk of cardiovascular events[72]. Nonetheless, overtreatment in the field of rheumatology should be prevented as far as possible. Two main factors could contribute to overtreatment in RA.

The first reason why a preventive intervention could lead to overtreatment is imperfect risk stratification. As shown in Table 2, the prior risks of developing clinically apparent arthritis or RA in the individuals

assessed across various RA prevention trials were variable but were rather low. If treatment to prevent RA is initiated in individuals with a prior risk of 20%, 1 out of 5 individuals will be correctly treated and 4 out of 5 individuals will be treated who would never have developed RA. Therefore, care must be taken not to confuse being at risk with having a diagnosis of RA. Otherwise, the incidence of the disease will simply quadruple by counting the at-risk individuals. The second reason relates to delay in treatment cessation: currently, most rheumatologists are not used to stopping DMARD treatment after a short treatment period. When DMARD treatment is started earlier than currently recommended and not stopped, the duration of illness (defined as a chronic disease with treatment) is prolonged rather than shortened (as illustrated in Fig. 2). As a result, the opposite of what was originally intended is achieved. The addition of these two risks creates a worst-case scenario in which both the incidence of the disease and the duration of treatment are increased.

Hence, more evidence, careful reflection and further discussions are needed before interventions at too early a stage of disease enter clinical practice. Cost-effectiveness analyses should also be performed and the results of these analyses incorporated into the discussions (Box 1).

Conclusion

Hence, overall, the glass is half empty and half full for RA prevention in arthralgia. Upon reviewing the outcomes of all the recently (or soon to be) published prevention trials, no clear and irrefutable evidence has yet emerged that earlier initiation of the most commonly used DMARDs in the arthralgia phase permanently prevents RA. However, not all data are negative. The data suggest that abatacept does have an effect on the risk of RA and that methotrexate has lasting effects on the severity of subclinical joint inflammation (detected on imaging), symptoms, disability and workability. These latter beneficial effects were not limited to autoantibody-positive patients or patients who developed RA, but were also present in autoantibody-negative patients and in patients who did not progress to RA. Hence, beneficial effects were present for the majority of patients with CSA and subclinical joint inflammation.

These results can be considered as an important 'proof of concept'. To further improve the field, we need to recognize the (sub)stages from CSA to RA and the 'point of no return', as well as learn the immunobiological processes that are crucial for this irreversibility. Subsequently, new prevention trials need to be designed and conducted that give the right drug at the right moment in the right patient. In addition, efforts are needed to prevent future overtreatment. Most pressing seems the development of a method to measure effectiveness and to be able to stop DMARD treatment in time so that the disease duration is indeed shortened by earlier treatment and not, paradoxically enough, prolonged.

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Author contributions

All authors researched data for the article, contributed substantially to discussion of the content and reviewed and/or edited the manuscript before submission. H.W.v.S. and A.H.M.v.d.H.-v.M. wrote the article.

Competing interests

The authors declare no competing interests.

Additional information

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