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Prevention of rheumatoid arthritis: A systematic literature review of preventive strategies in at-risk individuals

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ABSTRACT

Background: Rheumatoid arthritis (RA) is an autoimmune disease characterized by symmetrical peripheral polyarthritis in the hands and/or feet, leading to long-term disability if not treated effectively. RA is preceded by a preclinical phase, in which genetically predisposed individuals accumulate environmental risk factors, and during which autoimmunity develops, followed by the emergence of non-specific signs and symptoms before arthritis becomes manifest. Early treatment in at-risk individuals – i.e. before the disease is fully established – has the theoretical potential to delay or prevent disease onset, with a positive impact on both patients' life and society.

Objectives: We aimed to understand the feasibility of preventive treatment in at-risk individuals, taking into account recently performed studies and ongoing clinical trials, as well as patient perspectives.

Methods: We performed a systematic literature review (SLR) on Medline and Embase, searching articles published between 2010 and 2021 with the following key-words: "Rheumatoid arthritis", "arthralgia", "pre-treatment" or "prevent".

Results: Our SLR identified a total of 1821 articles. Articles were independently screened by two researchers. A total of 14 articles were included after screening, and an additional 8 reports were manually included. We identified ten relevant clinical trials performed in at-risk individuals, or in individuals with undifferentiated inflammatory arthritis. Although no treatment was shown to prevent RA onset, early treatment with rituximab and abatacept delayed onset of full-blown RA, and both conventional and biological disease-modifying antirheumatic drugs (DMARDs) decreased disease-related physical limitations and increased DAS28-defined remission, at least temporarily.

Conclusions: This SLR demonstrates that early treatment of at-risk individuals may be effective in delaying RA onset, thereby decreasing disease-related limitations in individuals in the pre-clinical phase of RA. Whether this may ultimately lead to prevention of RA remains to be determined.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that affects 0.5–1% of the population worldwide [1,2]. The onset can occur at any age, with a mean around 40–50 years. RA is characterized by symmetrical peripheral polyarthritis in the hands and/or feet, usually accompanied by systemic inflammation and other clinical manifestations. In untreated or non-responsive patients the inflammatory process eventually results in joint destruction, in some cases resulting in severe disability [3,4]. RA is also associated with an increased risk of cardiovascular disease and interstitial lung disease [5,6]. RA has a big impact on both the individual and the society. While it is possible for some patients to reach remission, not all patients respond to treatment. In addition to the patients affliction this can result in loss of work

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productivity and impairment of social activities. Even those who do respond are subjected to life-long treatment with costly therapies.

There are two major subtypes of RA, based on the presence or absence of autoantibodies against specific antigens, most notably IgM-rheumatoid factor (RF) and antibodies against citrullinated proteins (ACPA). In general, ACPA-positive patients have earlier onset of disease (i.e. at younger age) than ACPA-negative patients, and often display a more severe clinical disease [7]. In line with this, ACPA-positive patients also have lower remission rates after initiation of disease-modifying anti-rheumatic drug (DMARD) treatment and more joint damage, although clinical manifestations at diagnosis are often indistinguishable between ACPA-positive and ACPA-negative patients [8].

In the evolution from healthy to full-blown RA different disease phases can be discriminated: an initial at-risk period (with genetic and/or environmental risk factors), a phase of clinically silent autoimmunity (e.g. the presence of ACPA), followed by clinically suspicious arthralgia (CSA), undifferentiated arthritis (UA), early RA, and established RA [9,10]. However, some phases might not be seen in all the patients. Seropositive and seronegative patients have overlapping but distinct risk factors [11]. The preclinical at-risk phase of seropositive individuals is characterized by immune system activation, production of autoantibodies and non-specific musculoskeletal signs and symptoms, mostly arthralgia [12]. Moreover, individuals may experience fatigue, pain, and transient swelling of the joints [13]. Both circulating antibodies and high levels of C-reactive protein (CRP), indicating some level of systemic inflammation, can be found up to five years before RA onset and signify an elevated risk of developing RA [14,15].

Both ACPA-positive and ACPA-negative patients may have a symptomatic stage before developing overt clinical arthritis, which is characterized by the presence of arthralgia and/or subclinical inflammation and other circulating auto-antibodies in the seropositive patients. In the CSA phase, ACPA-positive and ACPA-negative patients have somewhat different clinical manifestations, with fewer tender joints but more rapid progression to RA in ACPA-positive patients [16]. The identification of seronegative at-risk individuals in the pre-clinical stage before the manifestation of arthritis is quite challenging and therefore most trials aimed at prevention of RA focus on seropositive at-risk individuals.

In the time preceding disease manifestation and in the earliest stages of disease, T cells shift towards a pro-inflammatory phenotype, with accumulation of expanded T cells in the synovium and increased levels of serum pro-inflammatory cytokines, including IL-2 [17–20]. B lineage cells are also altered in pre-RA individuals, with high levels of IgA plasmablasts in the peripheral blood [21]. Moreover, patients develop anti-modified protein antibodies (AMPA) against post-translationally modified proteins, such as acetylated and carbamylated proteins, closer to disease onset [22,23]. These findings suggest that the immune system is already derailed years before RA onset, which would potentially allow for targeted interventions to prevent or at least delay disease onset.

It has been shown that early treatment initiation in RA patients improves disease signs and symptoms, with lower disease scores and improved physical functioning as well as reduced radiographic progression [24]. Many patients also experience a rapid decrease in their work ability before treatment initiation and although treatment was unable to reverse disease-associated disability, it stabilized the need for sick leave and prevented incapacity for work [25]. Treatment in the preclinical phase of disease might lead to less complaints in the arthralgia phase, prevention of joint damage and improved work ability.

In order to prevent disease development it is important to identify which patients would benefit the most from a targeted intervention since on average only 30% of seropositive individuals will develop RA, and since many different factors influence disease risk [26,27]. Family history of RA is associated with increased disease risk by three to ten times [28,29]. Genetic predisposition, such as the presence of specific alleles in the HLA-DRB1 locus called shared epitope (SE), and environmental exposure both have a role in disease risk [30]. One of the main disease risk factors in seropositive individuals is smoking which significantly increases the risk of progression towards RA (and this risk may persist for some years after smoking cessation) especially when paired with SE [10,31,32]. Additional environmental risk factors are an unhealthy diet, obesity, lack of exercise, and stress, while moderate alcohol consumption may be a protective factor [33–36]. The stratification of at-risk individuals based on their risk factors may allow the identification of those patients who might benefit the most from early preventive actions and/or pharmaceutical interventions. Indeed, in one prediction model which used demographic, clinical, and serological data, patients were stratified into three categories based on their risk of developing RA. Individuals in the low-risk group had only 12% probability of developing RA in the next 5 years. This probability increased to 81% in the group with high risk, identifying the patients who might benefit the most from early intervention strategies [37].

At the moment, no formal treatment recommendations exist for individuals in the pre-clinical stage of RA after presenting with arthralgia; patients are monitored, but as a rule they do not receive any DMARD treatment until clinical signs and symptoms of arthritis and/or formal diagnosis of RA is established. The current study was designed to better understand the feasibility of interventional studies in at-risk individuals, taking into consideration both patient perspectives and the results of recently performed or currently ongoing intervention trials. We distinguished true preventive trials, in which at-risk individuals, including those with CSA, who did not experience clinical arthritis yet, were subjected to targeted interventions, from very early treatment strategies in which UA or early RA patients received treatment. We took note of the SLR and meta-analysis by Hilliquin et al. from 2018, which addressed the same but felt that the number of original reports published since then warranted a renewed investigation [38].

2. Methods

2.1. Search strategy

We performed a systematic literature search on Medline and Embase; we focused on articles published between 2010 and 2021. The keywords we used were the following: “exp Arthritis, Rheumatoid/ or ((rheuma* adj3 (gout or disease* or arthritis)) or RA).ti,ab,kf”; “pretreatment or early or suspect or probable or (preclinical or onset or profylaxis or pretreatment or arthralgia)).ti,ab”; “(prevent* or remission or progression).ti,ab,kf”.

2.2. Study selection criteria

We selected papers that reported randomized controlled trials (RCTs), trial protocols, summary of trials, and patients' prospective on the topic. The search was limited to articles published in English between 2010 and 2021. Articles were independently screened by two researchers (GF, AM) based on title and abstract, followed by full text. Selected articles were divided into three categories depending on their subject: background information, RCTs, and patient perspectives. Additional articles, conferences abstracts and reports were manually included after the search by the authors. The search, screening, and articles inclusion were done accordingly to the Cochrane Collaboration guidelines for a systematic literature review on interventions [39].

2.3. Summary of results

A total of 1821 articles were screened, following the before mentioned criteria. Of those, 18 duplicates and 122 papers in non-English were removed. Thus, a total of 1681 articles were eligible for inclusion. At the end of the first screening step, 22 articles were included and 8 additional relevant reports were added. Hand-selected reports included published articles and abstract presented at conferences. After the second screening phase, 8 articles were excluded, for a final count of

22 articles. Fig. 1 reports a summary of the search and inclusion process.

3. Results

3.1. Retrieved articles

Our search identified a total of 14 articles, which included RCTs, patients' perspectives, and literature overviews of our topic. Six additional articles (five trials and one patients' perspective study), one abstract and results presented at the Advances in Targeted Therapies meeting that took place in Marseille, France in March 2022 were included manually by the authors.

3.2. Randomized-controlled trials

In total, we thoroughly reviewed ten RCTs (Table 1):

- one RCT in seropositive first-degree relatives of RA patients, who were treated with conventional synthetic (cs)DMARD (StopRA study),
- six RCTs in arthralgia patients, where participants were treated with glucocorticoids (dexamethasone trial), csDMARDs (TREAT EARLIER study), biological (b)DMARDs (ARIAA trial, APIPPRA trial, PRAIRI trial), and statins (STAPRA study),
- two trials in UA, in which patients were treated with csDMARDs (PROMPT study) and bDMARDs (ADJUST trial),
- one trial in inflammatory arthritis, in which patients were treated with glucocorticoids (SAVE study).

Fig. 2 shows the timeline (Fig. 2a) of the included trials and their distribution in relation to the different (pre-clinical) phases of RA (Fig. 2b).

3.3. Glucocorticoids

Glucocorticoid are immunosuppressive and anti-inflammatory drugs which inhibit leukocyte migration to the site of inflammation and production of pro-inflammatory cytokines and soluble factors [40]. Glucocorticoids are used as first line medication in the treatment of RA, especially as bridging and/or local therapy in combination with cDMARDs [41,42]. They are also frequently used during flares, given

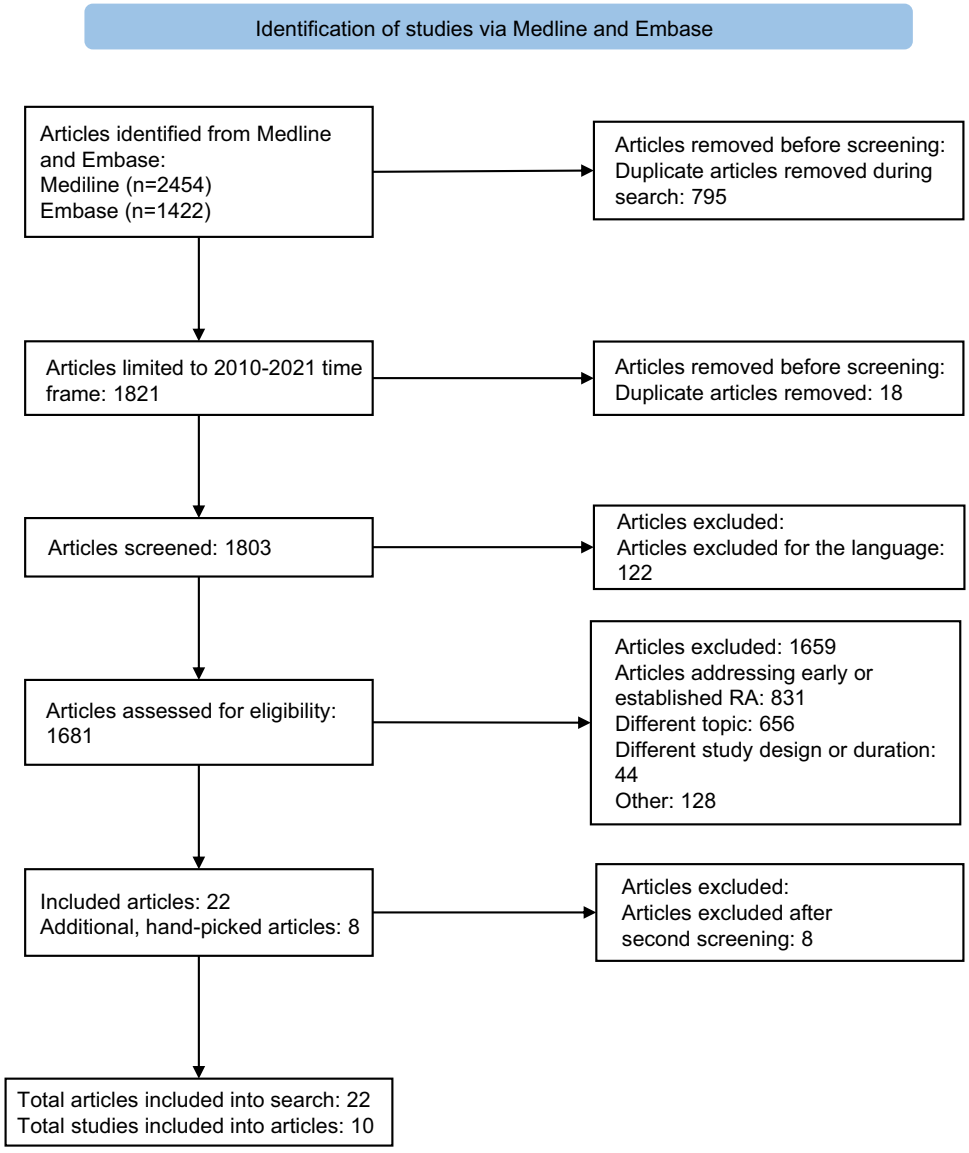


Fig. 1. Flow of articles inclusion. Papers were collected according to the search strategy described in methods, and screened by two independent reviewers (AM and GF).

Table 1
Summary table of preventive interventional trials in individuals at risk of developing rheumatoid arthritis.

Trial name	Inclusion criteria	Number of patients (treatment vs placebo)	Intervention	Time of follow-up	Primary outcome	Secondary outcome	Results	Reference
ADJUST study	- UA - ≤3 criteria for RA - Clinical synovitis - ACPA positivity - Symptoms <18 months	56 patients 26 treatment vs 24 placebo	8 infusions of 10 mg/kg of abatacept (10 mg/kg) for 6 months	- 6 months - 1 year - 2 years	- RA progression as per 1987 ACR criteria at 1 year	- Radiographic assessment of hands/wrists and feet at 6 months, 1 and 2 years - MRI of hand/wrists at 2 weeks, 6 months, and 1 year - ACPA and RF levels at 6 months and 1 year - DAS28 score based on CRP levels - Swollen and tender joints (28-joint count)	- Decreased but not significant RA progression in treatment group (46.2%) vs placebo (66.7%) - Improved osteitis, erosion, and synovitis at 6 and 12 months in treatment vs worsening of scores in placebo - Decreased ACPA positivity at 6 months (90.9%) and 1 years (86.7%) - DAS28-defined remission at 6 months (71.4% vs 35%) and 1 year (47.4% vs 27.4%) - Higher percentage of patients without swollen cells at 6 months (62.5% vs 14%) and 1 year (30% vs 14%)	(57, 58)
APIPPRA study	- CSA - ACPA and RF positivity or high ACPA serum levels	206 patients	125 mg weekly abatacept for 1 year	- 52 weeks - 2 years	- Feasibility, efficacy, and acceptability of treatment - Characterization of immune response - Time to development of clinically apparent synovitis in ≥3 joints or RA per ACR/EULAR 2010 criteria	- RA progression - Disease activity - Percentage of patients requiring DMARDs - Adverse events - Patients' perception	- Study concluded. Results expected in 2022	(62)
ARIAA study	- Arthralgia - ACPA positivity - Subclinical inflammation (tenosynovitis, synovitis, or osteitis in MRI of the dominant hand)	98 patients (49 treatment vs 49 placebo)	125 mg weekly abatacept for 6 months	- 6 months - 18 months	- Proportion of patients with improvement of synovitis or osteitis with MRI of dominant hand at 6 months	- Synovitis score at 12 and 18 months - Percentage of patients with new arthralgia - Pain score - MRI improvement - Swollen and tender joint - Percentage of patients with RA - DAS28 score	- Decrease in at least one of MRI parameters (tenosynovitis, synovitis or osteitis) at 6 months (62% in treatment vs 31% in placebo group) - Reduced RA progression at 6 months (8.2% vs 34%) and 1 year (35% vs 57%)	(59–61)
Dexamethasone study	- Arthralgia - 2× elevated IgM-RF and/or ACPA levels - HLA-DR SE	83 patients (42 treatment vs 41 placebo)	100 mg of dexamethasone at baseline and 6 months	- 6 months - 5 years	- 50% reduction of autoantibody levels or normalization at 6 months	- RA onset at 5 years (DAS28 or ACR 2010 criteria)	- Reduction of ACPA (22%) and RF (16%) at 1 month - ACPA reduction at 6 months - No difference in RA onset (20% in treatment vs 21% in placebo)	(47, 48)
PRAIRI study	- Arthralgia - ACPA and RF positivity - CRP > 0.6 mg/L - Subclinical synovitis (detected either by MRI with	81 patients (41 treatment vs 40 placebo)	100 mg methylprednisolone + single gift of 1000 mg rituximab at baseline	- 12 months - 18 months - 5 years	- Time to development of clinical arthritis	- Circulating autoantibody levels - Peripheral T and B cell numbers and subpopulations	- Decreased baseline risk of RA at 12 months (55% in treatment group) and 18 months (53%) - 12 month delay of RA development	(64)

(*continued on next page*)

Table 1 (*continued*)

Trial name	Inclusion criteria	Number of patients (treatment vs placebo)	Intervention	Time of follow-up	Primary outcome	Secondary outcome	Results	Reference
	gadolinium or ultrasound) - Absence of inflammatory arthritis						after rituximab treatment - Significant depletion of B cells - Significant decrease in IgA-RF, IgM-RF and total IgM after treatment	
PROMPT study	- UA	110 patients (55 treatment vs 55 placebo)	15 mg weekly methotrexate, increased every three months if DAS > 2.4	- 3 months - 6 months - 9 months - 12 months - 18 months - 30 months - 5 years	- Development of RA per 1987 ACR criteria	- Radiographic joint damage progression of hand and feet at all time-points except 3 months	- Delay in ACPA-positive, but not ACPA-negative, patients with high risk of RA at 1 year - No significant difference in RA onset and radiographic progression at 5 years	(49–52)
SAVE study	- Inflammatory arthritis <16 weeks	383 patients (198 treatment vs 185 placebo)	120 mg methylprednisolone at baseline	- 12 weeks - 52 weeks	- Clinical remission (no joint swelling, ≤2 tender joints, normalized CRP)	- Additional use of glucocorticoids or DMARDs	- No significant difference in remission (16.2% treatment vs 17.8% placebo) - Now difference in additional glucocorticoids (24.4% vs 27.0%) or DMARDs (43.4% vs 46.5%)	(46)
STAPRA study	- Arthralgia - ACPA LN or - ACPA and IgM-RF positivity	62 patients (31 treatment vs 31 placebo)	40 mg atorvastatin daily for 3 years	- 1 month - 6 months - 5 years	- Development of clinical arthritis (≥1 swollen joint out of SJC44)	- Development of RA per ACR/EULAR 2010 criteria	- Prematurely stopped – Treatment: 5–26 months follow-up; Placebo: 3–17 months follow-up - No significant difference in RA development (29% in treatment vs 19% in placebo group)	(68, 69)
Stop RA	- FDR - 2× elevated anti-CCP3 levels - Absence of clinical joint inflammation	114 patients	200–400 mg/daily Hydroxychloroquine for 1 year	- 52 weeks - 3 years	- RA progression as per ACR/EULAR 2010 criteria	- Change in disease activity (joint pain, swelling, stiffness, and fatigue) at 1 and 3 years - Changes in self-reported Physical, Mental and Social Health Quality of Life Measures at 1 and 3 years	- Waiting for results (primary completion date set for November 2023)	(40)
TREAT EARLIER	- CSA <1 year - Subclinical inflammation of hand/feet joints by MRI scan of hands or forefeet	236 patients (119 treatment vs 117 placebo)	120 mg methylprednisolon at baseline + increasing dose of methotrexate up to 25 mg/week	- 52 weeks - 2 years	- Clinical arthritis for ≥2 weeks - RA progression as per ACR/EULAR 2010 criteria - DMARD-free status	- Productivity and impairment scale - Symptoms (pain, fatigue, morning stiffness)	- No difference in RA onset - Delayed RA onset in subgroup of patients with high risk - Decreased joint inflammation by MRI in treatment group at 1 year -Decreased disease-related symptoms, physical impairment and loss of productivity in treatment group at 1 year	(53–55)

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. UA = Undifferentiated arthritis. RA = Rheumatoid arthritis. ACPA = Anti-Citrullinated Proteins Antibodies. ACR = American College of Rheumatology. MRI = Magnetic Resonance Imaging. RF = Rheumatoid Factor. DAS28 = Disease Activity Score of 28 joints. CRP=C-reactive protein. APIPPRA = Arthritis Prevention In the Pre-clinical Phase of RA with Abatacept. CSA = Clinical Suspected Arthralgia. EULAR = European Alliance of Associations for Rheumatology. DMARDs = Disease Modifying Anti-Rheumatic Drugs. ARIAA = Abatacept Reversing subclinical Inflammation as measured by MRI in ACPA positive Arthralgia. HLA = Human Leukocyte Antigen. SE = Shared Epitope. PRAIRI=Prevention of clinically manifest rheumatoid arthritis by B-cell directed therapy in the earliest phase of the disease. PROMPT = PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment. SAVE = Stop Arthritis Very Early. STAPRA = STAtins to Prevent Rheumatoid Arthritis. SJC44 = Swollen Joint Count among 44 joints. TREAT EARLIER = TREAT Early Arthralgia to Reverse or Limit Impending Exacerbation to Rheumatoid arthritis.

their rapid immunosuppressive action [43]. Side effects are dose- and time-dependent, and accordingly short-term and/or low dose administration of glucocorticoids ($\leq$ 5 mg/day) is associated with a lower risk of side-effects [43,44]. Therefore, the European Alliance of Associations for Rheumatology (EULAR) recommendations for the use of glucocorticoids advocate tapering as soon as possible [41]. In case of long-term use, a low dose ($\leq$ 5 mg/day) is preferred [45].

The Stop Arthritis Very Early (SAVE) trial investigated the efficacy of glucocorticoids in patients with early inflammatory arthritis of $\geq$1 joint. Patients were included if symptom duration was <16 weeks, and based on the number of swollen joints stratified into either monoarthritis or oligoarthritis ($\leq$ 3 swollen joints) or polyarthritis (> 3 swollen joints). Subsequently, patients were treated with either a single intramuscular injection of 120 mg methylprednisolone or placebo (NaCl 0.9%). Paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs) could be taken on demand. Patients were followed up for one year and the study's primary outcome was the presence of clinical remission at 12 weeks and at 52 weeks after injection, defined as the absence of joint swelling, not more than two tender joints and normalized CRP without additional glucocorticoid or DMARD treatment. A total of 383 individuals were included in the study and randomized to treatment (198 patients, 51.7%) vs. placebo (185 patients, 48.3%). No significant difference was found in the percentage of patients who reached remission in the two groups (16.2% in the treatment group vs. 17.8% in the placebo group). Moreover, no difference was found in the percentage of patients who required additional glucocorticoids (24.4% vs. 27.0%, respectively) or DMARDs (43.4% vs. 46.5%, respectively) in the two groups. Patients with monoarthritis had a statistically higher percentage of remission (27.7%) and lower symptom duration than patients with polyarthritis (10.2%), while no significant difference was found between the treatment groups [46].

The dexamethasone trial by Bos et al. recruited patients with arthralgia who had at least a two-fold increased level of IgM-RF and/or ACPA measured at least twice with an interval of >4 weeks. Patients were only included if positive for HLA-DR SE and were excluded in case of active hepatitis C and/or EBV infection, corticosteroid use or contraindications for their use, and co-morbidities that would decrease patients' life span. After inclusion, patients were randomized to receive 1–2 intramuscular injections (depending on the response to the first injection) of 100 mg of dexamethasone or placebo at baseline and at 6 weeks [47]. Eighty-three patients were recruited and randomized to active treatment (n = 42) vs. placebo (n = 41). The primary endpoint was a 50% reduction of antibodies or normalization after 6 months of treatment. The secondary outcome of this trial was RA development 5 years after treatment, based on the Disease Activity Score of 28 joints (DAS28) and the fulfilment of ACR criteria for classification. Although the primary endpoint was not reached (in each group only one patient reached the primary endpoint), the study did demonstrate a substantial reduction of ACPA (22% reduction in treatment group vs. 3% increase in placebo group) and, to a lesser extent, IgM-RF (14% reduction in treatment group vs. 1% increase in placebo group) after 1 month. ACPA reduction persisted for up to six months (13% reduction in treatment group vs. 12% increase in placebo group at 3 months, 8% reduction in treatment group vs. 2% increase in placebo group at 6 months), and IgM-RF reduction persisted up to three months (6% reduction in treatment group vs. 6% increase in placebo group), but neither ACPA nor IgM-RF reduction was associated with prevention or delayed onset of RA. The median follow-up time was 26 months, and no significant difference in RA development was observed in the two groups (20% in dexamethasone group, 21% in placebo group). Also, no significant difference in the median DAS28 score was found between the treatment (2.9; IQR 2.4–4.2) and placebo (3.7, IQR 3.2–4.1) groups [48].

3.4. csDMARDs

3.4.1. Methotrexate

Methotrexate has been the cornerstone of RA treatment for decades [41] and rheumatologists have ample experience with this drug, which has a favorable efficacy and safety profile. Consequently, it is not surprising that interventions with this csDMARD have been performed in the early and preclinical phases of the disease as well.

The PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment (PROMPT) study was not a true prevention trial as it evaluated the efficacy of methotrexate treatment in patients with UA, regardless of their ACPA status. Patients had symptoms for <2 years and were also DMARD-free [49]. The patients (110 patients in total; 55 patients in each arm) were randomized to either receive active treatment or placebo regardless of their specific risk for developing RA. Initial treatment was with methotrexate (15 mg/week) and the dosage was increased every three months if DAS was >2.4. After 1 year, treatment was discontinued and patients were followed for 60 months. The primary outcomes were progression to RA, defined by the 1987 ACR criteria, and radiographic joint damage of the hand and feet joints [50]. After trial conclusion, a risk stratification score was applied to the results based on a validated prediction model, and patients were stratified based on their risk [51,52]. Only patients with a high risk of developing RA were considered in the analysis after stratification [52]. The PROMPT study found that methotrexate treatment delayed RA onset in ACPA-positive, but not in ACPA-negative patients. Without risk stratification, no difference was found in the number of patients who developed RA in the treatment arm compared to placebo [50]. Upon risk stratification and selection of the patients with highest risk of developing RA (11 patients in each arm), a 1-year course of methotrexate reduced the absolute risk of developing RA by 45%, with more frequent drug-free remission after 5 years compared to placebo [52]. However, there was no significant lasting effect of methotrexate at 5 years after treatment [49].

The TREAT Early Arthralgia to Reverse or Limit Impending Exacerbation to Rheumatoid arthritis (TREAT EARLIER) study recruited patients with CSA and arthralgia for <1 year coupled with subclinical inflammation of the small joints of either hands or feet, as identified by unilateral MRI findings. Patients were treated with a single intramuscular dose of 120 mg methylprednisolone followed by methotrexate in increasing dosages up to 25 mg/week for 1 year, versus placebo for both, in a double-blinded manner. In the last 4 weeks of treatment, methotrexate was gradually reduced before being stopped at week 53. Patient recruitment was independent of their serological status (i.e. both RF/ACPA positive and negative individuals were included as long as they were at risk) and they were followed for an additional year. The primary endpoint of the study was either development of clinical arthritis that lasted $\geq$2 weeks or RA by the American College of Rheumatology (ACR)/ EULAR 2010 RA classification criteria. The study's co-primary

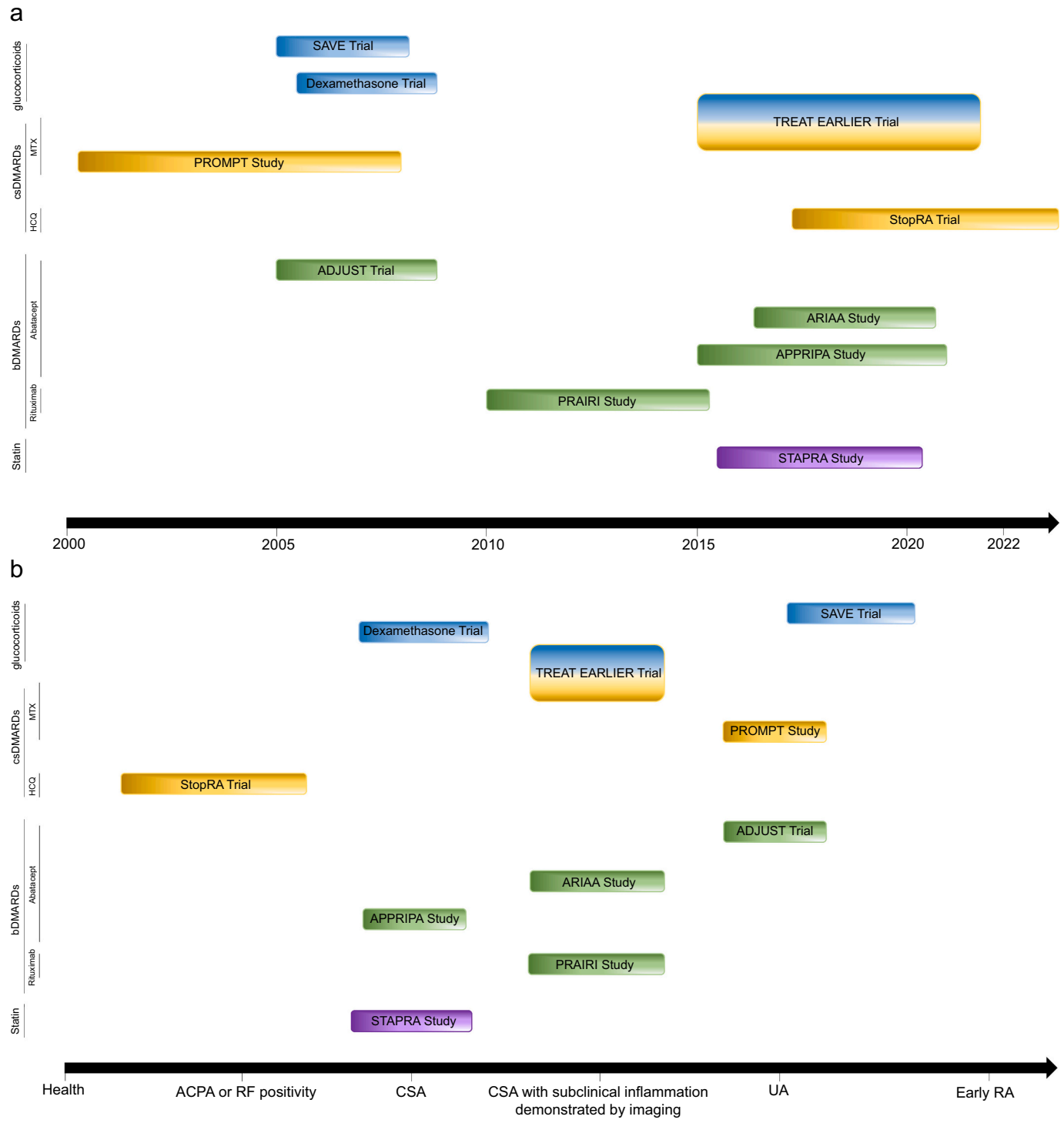


Fig. 2. Overview of preventive interventional trials. In blue trials investigating glucocorticoids, in yellow conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs), in green biological (b)DMARDs, and in purple statins. HCQ = hydroxychloroquine. ADJUST = Abatacept study to Determine the effectiveness in preventing the development of rheumatoid arthritis in patients with Undifferentiated inflammatory arthritis and to evaluate Safety and Tolerability. APIPPRA = Arthritis Prevention In the Pre-clinical Phase of RA with Abatacept. ARIAA = Abatacept Reversing subclinical Inflammation as measured by MRI in ACPA positive Arthralgia. PRAIRI=Prevention of clinically manifest rheumatoid arthritis by B-cell directed therapy in the earliest phase of the disease. PROMPT = PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment. SAVE = Stop Arthritis Very Early. STAPRA = STAtins to Prevent Rheumatoid Arthritis. TREAT EARLIER = TREAT Early Arthralgia to Reverse or Limit Impending Exacerbation to Rheumatoid arthritis. **(A)** Timeline of preventive interventional studies. **(B)** Overview of preventive interventional trials based on their target population. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

endpoint was DMARD-free status for two years, and secondary endpoint was patient functioning, assessed by Health Assessment Questionnaire disability index (HAQ-DI) and Work Productivity And Impairment (WPAI), as well as symptoms (pain, fatigue, morning stiffness) at baseline and regular 4 month intervals after treatment initiation [53,54]. Joint inflammation was explored using MRI at baseline and 4, 12, 24 months after treatment initiation. A total of 236 participants (119 participants in the treatment group, 117 in the placebo group) were included in the study; three participants were lost to follow-up in the treatment group, while 5 participants were lost in the placebo group. Treatment with methotrexate did not prevent RA onset (20% of RA onset in treatment group vs. 18% in placebo group), although decreased joint inflammation was detected by MRI during treatment and up to a year after treatment was stopped (mean difference of −1.4 points). Moreover, patients treated with methotrexate had reduced disease-related symptoms (pain = −8 on 1–100 scale in treatment vs placebo, morning stiffness = −12, and functional impairment), less physical limitations and less loss of work productivity, regardless of their autoantibody status. High risk participants, who had a risk of developing RA higher than 70% at baseline, also had a delay in RA onset during treatment, although disease frequency was similar at 2 years after treatment initiation (67% in both groups) [54,55]. Interestingly, most beneficial effects occurred in the first 4 months and were sustained throughout the rest of the study despite a moderate target dose treatment adherence of 53% at 52 weeks in the methotrexate group.

3.4.2. Hydroxychloroquine

Hydroxychloroquine is a weak basic that has been used for centauries as antimalarial drug. Hydroxycloroquine accumulates in the lysosome, interfering with its activity and autophagy, preventing immune cell activation and cytokine production. On T cells, hydroxychloroquine also causes reduction of CD154 expression [56].

The StopRA study is currently being conducted and focuses on first degree relatives of RA patients with serum levels of anti-cyclic citrullinated peptide (anti-CCP3) two or more times higher than normal, but without clinical joint inflammation. The study aims to recruit 114 participants, who are randomized to either receive 200–400 mg/daily hydroxychloroquine (based on ideal body weight) or placebo, for 12 months and followed for 2 additional years. The primary endpoint is the number of patients who progress to clinically apparent RA, defined by ACR/EULAR 2010 classification criteria. Secondary outcomes include changes in disease activity defined by joint pain, swelling, stiffness, and fatigue at 12 and 36 months, as well as self-reported Physical, Mental and Social Health Quality of Life Measures. Results should be available after the primary completion date by the end of 2022 [40].

3.5. Biological DMARDs

3.5.1. Abatacept

Abatacept is a human fusion protein of CTLA-4 and the Fc portion of IgG that targets CD80 and CD86 on antigen presenting cells, thereby preventing binding to CD28 expressed on T cells and subsequent activation of these cells via downstream signaling pathways [57].

The 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 (ADJUST) trial assessed the efficacy of abatacept in preventing RA in patients with UA/very early RA. Patients were considered eligible if they met a maximum of three criteria for RA diagnosis, as classified by ACR 1987 criteria, with concomitant symptomatic clinical synovitis. Moreover, all participants had circulating ACPA and symptoms for <18 months. Corticosteroids were allowed with a dose ≤10 mg prednisolone or equivalent, but no previous treatment with biological drugs or DMARD was allowed. Fifty-six patients were included in the study and stratified for the presence of erosions. Patients received intravenous abatacept (10 mg/kg) or placebo for six months (days 1, 15, 29, 57, 85, 113, 141, and 169), and were followed-up for 18 additional months [58]. The primary endpoint was RA diagnosis as defined by the 1987 ACR criteria. Additionally, radiographic progression (hands, wrists and feet), bone erosions, osteitis and synovitis (MRI of hand and wrist with the most prominent clinical synovitis), antibody levels, and DAS28 based on CRP levels were assessed. The percentage of patients in the abatacept group who developed RA at 1 year (46.2%) was numerically lower compared to placebo (66.7%) but the difference was not statistically significant. Moreover, abatacept treatment slowed radiographic progression and was associated with improved osteitis, erosion, and synovitis scores at 6 months and 1 year, while patients in the placebo group had worsening of their scores. ACPA positivity was reduced at 6 months (90.9%) and 1 year (86.7%) in the abatacept group, but remained unaltered in the placebo group. Abatacept also caused a decrease in the percentage of RF-positive patients at 6 months (59.1%) and 1 year (73.3%) in comparison with baseline (85.7%), which was not observed in the control group. Moreover, 71.4% of patients treated with abatacept had DAS28-defined remission at 6 months vs. 35.0% of placebo treated patients. This was also seen at 1 year (47.4% in abatacept group vs. 28.5% in the placebo group). Of the abatacept patients, 62.5% had zero swollen and tender joint after 6 months, which decreased to 30.0% at 1 year follow-up, whereas the proportion of patients in the placebo group with zero swollen and tender joints remained constant at 6 and 12 months (14.3%) [57].

The Abatacept Reversing subclinical Inflammation as measured by MRI in ACPA positive Arthralgia (ARIAA) study investigated the efficacy of abatacept in improving subclinical inflammation in ACPA-positive arthralgia patients as measured by the presence of tenosynovitis, synovitis, or osteitis on MRI of the dominant hand. Patients were randomized to receive either abatacept subcutaneously (125 mg weekly) or placebo (NaCl 0.9%) for 6 months, and were followed for an additional 12 months [59]. Ninety-eight patients received either treatment or placebo, and the study found a significant reduction in at least one MRI parameter (tenosynovitis, synovitis or osteitis) at 6 months in the treatment arm (62% in the abatacept group vs. 31% in the placebo group), indicating improvement in subclinical arthritis. Moreover, at 6 months, fewer patients in the abatacept arm (8.2%; 4 patients) developed RA compared to the placebo arm (34.7%; 17 patients) [60]. Reduced RA development in the treatment arm was still significant one year after stopping treatment (35% in the abatacept group vs. 57% in the placebo group) [61].

The Arthritis Prevention In the Pre-clinical Phase of RA with Abatacept (APIPPRA) trial is a similar study in patients with CSA and presence of both ACPA and RF or with high serum levels of ACPA alone (i.e. three times higher than the upper limit than normal (ULN)). Exclusion criteria include clinical evidence of joint swelling, previous diagnosis of autoimmune disease, use of corticosteroids within 12 weeks before inclusion used to treat musculoskeletal symptoms and current use of cs/bDMARDs. The study aims to recruit 206 patients who are randomized to either receive weekly subcutaneous injections of 125 mg abatacept for a year or placebo. Patients are followed up for an additional year after the end of treatment. The primary study endpoints are feasibility, efficacy, and acceptability of treatment, and the characterization of immune and inflammatory responses associated with ACPA for the duration of the therapy. Co-primary endpoints are the time to development of clinically apparent synovitis in at least three joints or time to development of RA as defined by the ACR/EULAR 2010 classification criteria. The secondary endpoints of the study are development of RA and assessment of disease activity, the percentage of patients requiring DMARDs, treatment adverse events, and patients' perceptions. Results are expected to be presented by the end of 2022 [62].

3.5.2. Rituximab

Rituximab is a chimeric monoclonal antibody that specifically targets CD20 on B cells, inducing cell death through complement-dependent cytotoxicity and antibody-dependent cytotoxicity [63].

In the Prevention of clinically manifest rheumatoid arthritis by B-cell directed therapy in the earliest phase of the disease (PRAIRI; "Prevention of RA by Rituximab") study, patients with arthralgia without clinical arthritis were treated with rituximab, causing B cell depletion. Patients had to be positive for both ACPA and IgM-RF, but could not have experienced inflammatory arthritis nor received DMARDs in the past. Additional inclusion criteria were detectable CRP at screening with levels higher than 0.6 mg/L (the lower level of detection of high sensitivity CRP assay) or subclinical synovitis as detected either by ultrasound or MRI with gadolinium. Eighty-one patients were recruited in the study and randomized to receive 100 mg methylprednisolone followed by either a single infusion of 1000 mg rituximab (41 patients) or placebo (NaCl 0.9%; 40 patients). Patients were stratified for age ($<$ 40 years old, or $\geq$ 40 years old) and sex before randomization, with a scheduled follow up of five years after the intervention. The primary outcome of the study was the time to development of clinical arthritis, defined as swollen and tender joints as observed by two independent investigators. Moreover, the study investigated circulating autoantibody levels and peripheral B and T cell numbers and subpopulation composition through fluorescence-activated cell sorting (FACS) analysis. Rituximab treatment was associated with a reduction of the baseline risk of developing RA at 12 months (55% reduction of risk compared to placebo group) and at 18 months (53% reduction of risk compared to placebo). Moreover, patients treated with a single infusion of rituximab had a delay of RA development of 12 months at the point when 25% of the subjects had developed arthritis ("25th percentile"). In contrast, at the end of follow-up time, the risk of RA development was not statistically significant different between treatment and placebo (34% after a median of 16.5 months vs. 40% after a median of 11.5 months, respectively). In summary, the PRAIRI study demonstrated that depletion of B cells in individuals with arthralgia significantly delayed RA onset, confirming that B lineage cells play an important role in disease pathogenesis, including progression to clinical overt RA [64].

3.6. Other strategies

3.6.1. Statins

Statins are lipid-lowering agents with a good safety profile and anti-inflammatory properties: in RA patients, statins improved disease activity scores and caused decreased inflammatory parameters [65]. Additionally, in mice models of RA, statins had a protective effect against disease development, and on a population level, statin use is associated with a reduced risk of developing RA [66,67]. Hence, statins were postulated to have a possible beneficial effect in preventing RA [68].

The STAtins to Prevent Rheumatoid Arthritis (STAPRA) trial investigated the ability of a statin to prevent development of RA in high risk individuals with arthralgia. Patients were required to have either high levels of ACPA (three times the ULN) or both ACPA and IgM-RF positivity without (a history of) arthritis, and were randomized to receive either 40 mg of atorvastatin or placebo daily for 3 years [69]. The primary outcome of the study was development of clinical arthritis, defined as one or more swollen joints out of 44 joints assessed (SJC44). A secondary outcome was the development of RA as defined by the ACR/EULAR 2010 classification criteria. The study was prematurely stopped due to recruitment difficulties, with a total of 62 patients out of 220 originally planned. 36% of patients in the placebo arm and 19% of patients in the atorvastatin arm dropped out of the study, mainly due to (perceived) side effects. The most common side effect in both groups was muscle pains or cramps (37%). The median duration of treatment was 8 months (5–26 months in the atorvastatin group, 3–17 months in the placebo group) and median follow-up time was also similar between the two groups (17 (IQR 6–28) months for atorvastatin, 14 (IQR 5–36) months for placebo). No significant difference was found in the percentage of patients who developed arthritis (29% in the atorvastatin group vs. 19% in the placebo group) or fulfilled the 2010 ACR/EULAR classification criteria for RA (26% in the atorvastatin vs. 19% in the placebo group). With the limited number of participants, the study was underpowered and formally inconclusive, but the fact that *more* patients developed RA in the intervention group makes it very unlikely that a true preventive effect exists [68].

3.7. Individual perspectives of at-risk individuals on early and preventive treatment

Studies on patient preferences with respect to clinical trials have also investigated the likelihood of patients to participate in preventive studies, as well as what requirements are necessary for participation. Patients with a lower risk of developing RA were less inclined to partake in preventive trials than patients with CSA [70]. Moreover, a $\geq$ 20% decrease of RA risk was associated with increased willingness to undergo treatment when the probability of serious adverse events was $\leq$10% [71]. Similarly, van Boheemen et al. showed that the willingness to use preventive medications increased from 53% to 69% in at-risk individuals when the disease risk increased from 30% to 70% risk [72]. This clearly indicates that patients require a better understanding of their own risk in order to make decisions regarding preventive treatment. Importantly, this requires personalized risk communication that needs to be understandable for the patient, tailored to their social status and education [70,73]. While effectiveness of treatment has a positive impact on patients' willingness to take medication, perceived risk of side-effects has a negative impact: patients are less likely to participate if the achieved benefit is lower than the perceived expected benefit. Moreover, patients prefer and are more likely to adhere to lifestyle modifications than pharmacological therapies, and have a positive perception of interventions that might lead to substantial decrease or even complete elimination of disease risk. Additionally, treatment needs to be safe and a non-invasive route of administration (i.e. oral tablet taken at home) was usually preferred, to the point that this aspect might influence patients' perspective on preventive treatment more than the efficacy of the intervention in preventing RA [72,74,75].

4. Discussion and future perspectives

Preventive strategies focus on the prevention or delay of disease onset. While the concept of preventive therapies is not novel, no clear strategy has yet emerged for the prevention of RA. We systematically reviewed the literature for interventional studies in individuals with either high-risk of RA, UA or very early RA. In the past years, several clinical trials have investigated the safety and effectiveness of early (preventive) treatment in RA, focusing on individuals who were at high risk for disease without a clinical diagnosis (true prevention) and patients with very early disease (UA or early RA). These trials investigated a wide range of drugs, such as glucocorticoids, cs/bDMARDs and statins, some of which are used in clinical practice for disease management. Several of these trials showed that early treatment with csDMARDs and bDMARDs may transiently increase the likelihood of drug-free remission and reduce physical limitations in both arthralgia and UA or very early RA patients. Thus, while glucocorticoids did not have a significant effect on disease prevention, studies focusing on csDMARDs or bDMARDs were able to demonstrate some efficacy of treatment.

An important aspect of preventive trials is their feasibility, both in terms of safety, efficacy, and willingness of patients to participate. At-risk individuals are less likely to participate in trials and to adhere to treatment when largely asymptomatic. Both the STAPRA study and the PRAIRI trial faced difficulties in patient recruitment, which led to early interruption of the study (STAPRA, only 62 participants included out of 175 found eligible), or a reduction in sample size (PRAIRI, 81 participants out of 90 patients planned, due to slow inclusion rate) [64,68]. This reduction in the number of participants poses a serious problem, because it may lead to loss of statistical significance (type 2 statistical error). Tailored educational strategies might be required to improve

individuals' awareness and their predisposition towards preventive studies as patients are more inclined to participate when well-informed and if the risk of RA is strongly reduced by an intervention with limited side effects. The involvement of general practitioner might help increase inclusion rates, since they could approach patients in the earliest stages of risk, even before arthralgia or UA manifest. Moreover, the establishment of a registry of at-risk individuals, such as the one created by the Rheuma Tolerance for Cure (RTCure) consortium, could help in the identification and inclusion of more patients in RCTs [76].

It is clear that patients in the earliest stages of disease benefit the most from preventive strategies [77], and are more likely to have a delay or reduced risk of disease progression upon treatment, as demonstrated by the ARIAA and the PRAIRI study. This points out that early identification of at-risk individuals is of paramount importance. This naturally leads to the need to define specific stratification criteria to select patients, as well as a redefinition of primary study outcomes. In addition, to delaying the onset or preventing RA, a secondary goal of therapy could be to improve quality of life in the preclinical phase of the disease, as was observed in the TREAT-EARLIER trial, and/or to positively alter the disease course if the patient does ultimately develop RA; for example, such a treatment might increase the likelihood to achieve DMARD-free remission or improve the health-related quality of life. Interestingly, in several trials (PRAIRI, ARIAA, and TREAT-EARLIER) certain beneficial effects persisted for $\geq$6 months after treatment cessation pointing towards the fact that control of inflammation very early in the disease course can result in long-lasting improvement of signs and symptoms.

Of note, a good balance between under- and overtreatment is essential when developing preventive strategies in at risk individuals who are strictly speaking not yet patients, since they have not manifested clinical arthritis [78].

Furthermore, the type of intervention that is effective may also differ across the various preclinical phases of the disease. In the coming years research efforts should be steered towards better understanding the immune alterations in the preclinical phase of RA, for instance by investigating various compartments of the immune system, i.e. not only peripheral blood but also lymph nodes and the bone marrow. Early targeted intervention could result in beneficial effects larger than the effects of treatment initiated at the time of diagnosis (i.e. prevention of structural damage, reduced disability, higher (drug-free) remission rates, etc.). Numerous components of disease pathogenesis could serve as potential prevention targets, including autoantibody generation, inflammation and the immune response. Possible future treatment strategies are the delivery of tolerogenic therapies through nanoparticles, cellular therapies with tolerogenic antigen-presenting cells (i.e. dendritic cells), regulatory T cells and mesenchymal stem cells, immune checkpoint receptor agonists (i.e. PD-1, CD200R or BTLA stimulation) and co-stimulatory molecule blockade, as well as depletion strategies for (subsets of) T and B cells [79].

In summary, several preventive strategies have been shown to delay RA onset when applied in the early stages of the disease and to decrease disease burden at least temporarily, while true prevention has hitherto not (yet) been achieved. Results from ongoing studies are expected to support and increase our knowledge of disease prevention as well as advance our understanding of the pathophysiological mechanisms underlying RA. Strategies for patient identification and stratification, as well as tailored education and treatment, are also necessary to ultimately reach the goal of disease prevention.

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Author's contribution

GF and AM independently screened and selected the articles identified by RS's search strategy. All authors contributed to the design, literature review and drafting of the manuscript, and approved it for publication.

Declaration of Competing Interest

SWT and NdV were involved in the PRAIRI trial and are co-authors on the publication.

Data availability

No data was used for the research described in the article.

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