Ann Rheum Dis 84 (2025) 521–528

Contents lists available at ScienceDirect

Annals of the Rheumatic Diseases

journal homepage: https://www.sciencedirect.com/journal/annals-of-the-rheumatic-diseases

Viewpoint

How to treat undifferentiated arthritis today or tomorrow? A consideration of treatment recommendations in light of current evidence

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ARTICLE INFO

Article history:
Received 23 September 2024
Received in revised form 3 December 2024
Accepted 7 January 2025

ABSTRACT

Patients with undifferentiated arthritis (UA) have clinically apparent inflammatory arthritis but no evident diagnosis or classification. Considering UA as a definition 'per exclusionem' implies that the population designated by this term is affected by changes in the way other diseases, eg, rheumatoid arthritis (RA), are classified or diagnosed. Current treatment recommendations for UA are largely similar to recommendations for RA. The recommendations are based on the idea that UA is an early stage of RA and on literature generated in the 2000s before the development of the 2010 classification criteria for RA. However, conventional UA (so-called '1987-UA') is presumably different than contemporary UA ('2010-UA'). Strikingly, there are no randomised placebo-controlled trials done on '2010-UA,' and this poses questions on whether the recommendations for UA are still valid. In this absence, we assume that treatment recommendations from '1987-UA' can be extrapolated to '2010-UA' if (1) essential patient characteristics are the same, (2) long-term outcomes are similar, (3) prognostic factors are largely the same, and (4) there are indications from research other than placebo-controlled randomized clinical trials (RCTs) that disease modifying antirheumatic drug (DMARD) treatment in 2010-UA is effective. We evaluate these requirements one by one based on the literature on 2010-UA. This reveals that 2010-UA is milder in initial presentation and disease outcomes than 1987-UA. Today's UA population is >95% anticitrullinated protein antibody-negative, presents with mono- or oligoarthritis, frequently achieves spontaneous remission, and rarely progresses to RA. We suggest that 2010-UA is a distinct patient group within the early arthritis spectrum, requiring additional research, after which recommendations may need to be updated.

INTRODUCTION

Undifferentiated arthritis (UA) is a concept we think we know. Patients present with clinically apparent inflammatory arthritis (joint swelling at physical examination) and have no clear diagnosis or classification. It is, therefore, also called unclassified arthritis. We recognise that this population is, to some extent, heterogeneous by the nature of the potential underlying diseases it may evolve to, the uncertainty about self-remittance, and the unclear amount of investigative effort needed to robustly claim 'unclassifiability.' Though treatment recommendations are clear and included in the 2016 European Alliance of Associations for Rheumatology (EULAR) recommendations for early arthritis [1]. These state that (1) if a definite diagnosis cannot be reached and the patient has early UA, risk factors for persistent and/or erosive disease, including the number of swollen joints, acute phase reactants, rheumatoid factor (RF), anticitrullinated protein antibodies (ACPAs), and imaging

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Handling editor Prof Kimme Hyrich.

https://doi.org/10.1016/j.ard.2025.01.036

findings, should be considered in management decisions, (2) patients at risk of persistent arthritis should be started on disease modifying antirheumatic drugs (DMARDs) as early as possible (ideally within 3 months), even if they do not fulfil classification criteria for inflammatory rheumatologic disease, (3) among the DMARDs, methotrexate is the anchor drug and, unless contraindicated, should be part of the first treatment strategy in patients at risk of persistent disease, and (4) the main treatment goal is to achieve clinical remission, assessed with regular monitoring of disease activity. Thus, the EULAR recommendations endorse treatment for UA that is very similar to treatment for rheumatoid arthritis (RA).

It is known that recommendations are intended as support and that deviations from these recommendations can be made for individual patients. Because recommendations are generally based on scientific data, the question of how to manage UA, therefore, does not appear to be a recent or pressing issue. The question is, is that true? Are current recommendations still sufficient for patients with UA today or tomorrow? We will here evaluate the concept of UA, its evolvement over time, and the evidence we have regarding prognostication and intervention.

UA AND ITS HISTORY

The first naming of the term UA occurred in the late 1980s [2]. It was described as a group of patients with early arthritis for whom no clear diagnosis could be made. In that respect, the description of the entity is not substantially different from the current description. It was and still is clearly a diagnosis by exclusion. Over the past 30 years, classification criteria for several inflammatory arthritides have changed, of which changes in the classification criteria for RA may have the most numerical impact on UA. Although classification criteria are not intended as a diagnostic tool, these changes do influence the general concept of a disease.

In the first description of UA in the late 1980s, RA was excluded by referring to the 1958 ARA classification criteria. The number of studies on UA, which reflects interest in UA, began to increase from 2003 to 2005, with a peak in the number of publications in 2011. These figures suggest that the majority of studies on UA were conducted when RA was defined according to the 1987 classification criteria. A suggestion that is confirmed when reading the studies in more detail. The vast majority of studies on prognostic markers studied a UA population that had no clear diagnosis, including RA, according to the 1987 criteria. A widely used and extensively validated prediction model that estimated the risk of RA was also derived for the '1987-UA-population' [3−5]. The placebo-controlled randomised clinical trials done in UA are summarised elsewhere [6]. There are 5 trials on UA; all were designed and executed before 2010. Consequently, all trials were done in a 1987-UA population (except for the PROMPT trial, which used an even older definition and studied 1958-UA, at that time called 'possible RA'). The primary endpoint in all of these trials was the development of RA (according to clinical diagnosis without or with fulfilment of the 1987 criteria for RA).

As is known, the classification criteria for RA were changed again in 2010, with the aim of being able to recognise or classify RA earlier. Some of the patients that were formerly classified as UA are now characterised as RA; this mostly concerned ACPA-positive patients [7]. This has obviously changed the remaining group of UA patients (that we will refer to as '2010-UA' or 'contemporary UA').

DIAGNOSING UA

In clinical practice, we do not consider classification criteria (eg, for RA) to exclude other diagnoses and thereby identify patients with UA. There is also no recommendation on what diagnostic test should be done or what classifiable diseases should be ruled out before clinical arthritis can be labelled as undifferentiated. In daily practice, UA is therefore diagnosed by clinical expertise. A recent study covering UA patients diagnosed between 1993 and 2019 studied 'expertise-based UA' and showed that this UA population has changed over time [8]. This study illustrates that classification criteria influence what doctors consider a disease entity. More importantly, these results hint at the fact that we must pay close attention to whether the knowledge from the literature applies to today's patient group.

HOW TO MANAGE 2010-UA?

There is a paradox between the scientific data being largely based on the 1987-UA and the population of UA patients that we see in daily practice. Also, the above-mentioned EULAR recommendations for UA are based on studies that evaluated populations with early RA or early arthritis, and none of the studies referred to were done on 2010-UA [1]. Also, no placebo-controlled randomised clinical trials have been conducted on '2010-UA'/'contemporary UA.' The question is, therefore, whether the results of the prognostic studies and clinic trials in the 1987-UA population can be extrapolated to the current 2010-UA population.

In the absence of placebo-controlled randomised clinical trials in 2010-UA, we presume that the data from 1987-UA and recommendations for UA can be extrapolated to 2010-UA if (1) essential patient characteristics are the same, (2) long-term outcomes are similar, (3) prognostic factors are largely the same, and (4) there are indications from research other than placebo-controlled randomized clinical trials (RCTs) that DMARD treatment in 2010-UA is effective. We will consider these requirements one by one.

PATIENT CHARACTERISTICS HAVE CHANGED

Some classic characteristics that describe a rheumatologic patient population are the number of swollen and tender joints, their distribution at physical examination, and autoantibodies (ACPAs and RF) as laboratory results. Approximately 25% to 65% of 1987-UA patients are ACPA-positive [4,9−12]. Due to the composition of the 2010 classification criteria for RA, in which autoantibodies carry a heavy weight, ACPAs have become rare in 2010-UA. Only 4% to 5% of 2010-UA patients are ACPA-positive (Fig 1) [3,4,9−16].

The number of tender and swollen joints has also changed. The mean number of tender joints in 1987-UA ranged between 5 and 7, and the number of swollen joints between 3 and 6 [4,9−12]. In 2010-UA, in contrast, patients presented with, on average, 1 or 2 tender joints [13,14] and also 1 or 2 swollen joints (Fig 1) [8,13−16].

Other features, such as age, gender, and the frequency of increased acute phase reactants, remained largely unchanged. Hence, the majority of current UA patients are ACPA-negative and present with mono- or oligoarthritis (Fig 1).

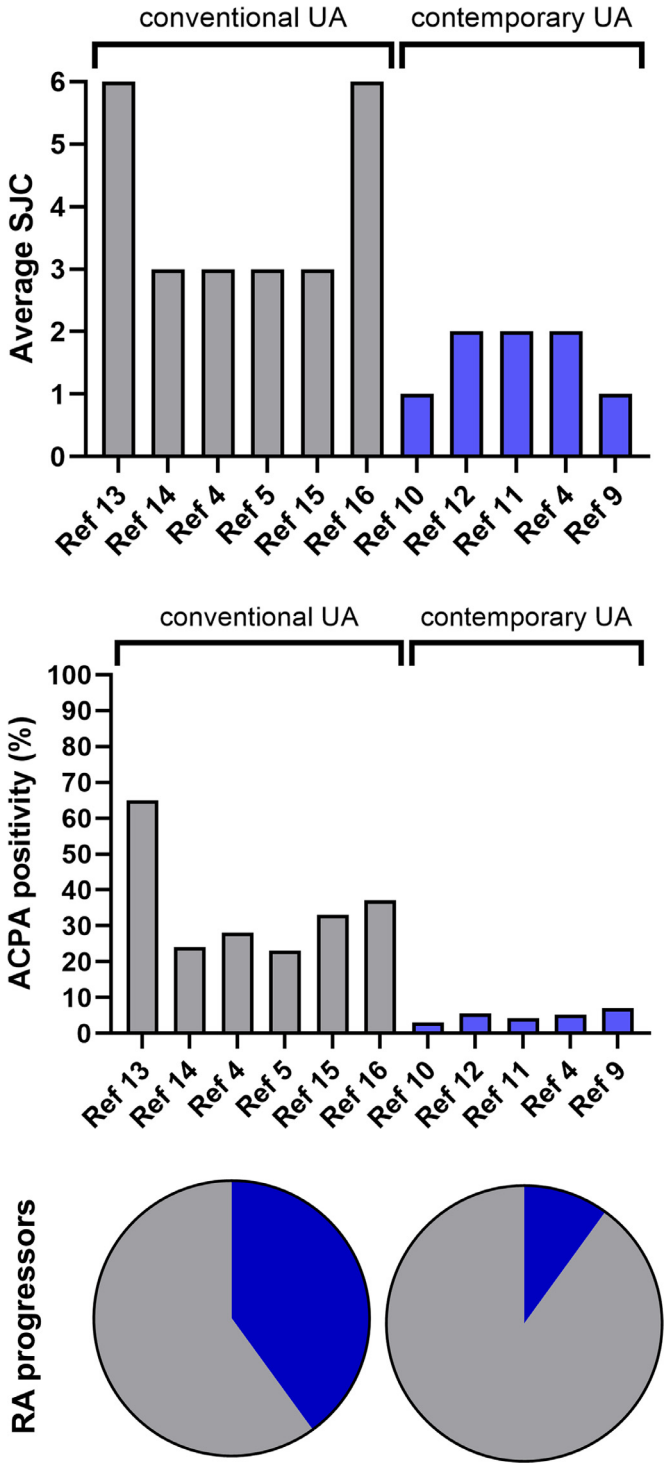

Figure 1. Average number of swollen joints (upper), percentage anticitrullinated protein antibody (ACPA) positivity (middle) , and percentage of patients progressing to RA (lower) in patients presenting with conventional undifferentiated arthritis (UA) ('1987-UA') and contemporary UA ('2010-UA'). The figures on the swollen joint count (SJC) and ACPA positivity are based on data from [3,4,9–16]. The percentage of UA patients that developed RA is indicated in blue and based on data from [4,14].

LONG-TERM OUTCOMES HAVE CHANGED

It is not surprising that as current UA comprises a different patient population, long-term outcomes differ as well. Compared with a previous rate of conversion to RA of 30% to 45% in 1987-UA [3,4], ≤10% of 2010-UA develops RA (according to the 2010 criteria) (Fig 1). RA development generally occurs within the first year [14]. Whether 1987-UA and 2010-UA differ in the course of disease activity score (DAS) and functional disabilities over time remains to be studied. Interestingly, a recent study revealed that about 60% of 2010-UA patients achieved sustained remission without DMARDs. This was defined as the sustained absence of swollen joints and included not only DMARD-free sustained remission but also spontaneous sustained remission (without ever DMARD treatment); this might be considered as resembling a cure [8]. Furthermore, in contrast to RA and 1987-UA, patients with 2010-UA have no excess mortality [13]. So, although some long-term outcomes remain to be studied in 2010-UA, available data suggest that the course of 2010-UA is more favourable than for 1987-UA, which in turn is also confirmatory that the 2010 RA criteria are capturing more patients with a poor prognostic phenotype: the 'RA phenotype.'

PROGNOSTIC FACTORS HAVE PARTLY CHANGED

Classic prognostic factors

Prognostic factors are generally studied with RA development as an outcome. The EULAR recommendation mentions swollen joints, acute phase reactants, RF, and ACPAs as key prognostic factors [1]. Radiographic erosions have also been shown to be predictive in 1987-UA [17]. Several of these classic risk factors are less informative in 2010-UA. ACPAs are still predictive, but considering their frequency of <5%, it is less clinically relevant [14,15,18]. Raised acute phase reactants (C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR)) are no longer predictive of RA development [14,15]. Polyarthritis remains a predictor for RA development but has also become infrequently present [14,15]. In addition, its value is slightly dependent on the outcome. When considering disease persistence as a long-term outcome, polyarthritis was no longer an independent risk factor [13]. Radiographic erosions are also not predictive in 2010-UA [17,18]. Thus, several classic risk factors are no longer relevant in 2010-UA. The presence of ACPAs remains the most consistent

Table 1
Prognostic factors in conventional undifferentiated arthritis (1987-UA) and contemporary undifferentiated arthritis (2010-UA)

Prognostic factor	Outcome: development of RA		Outcome: persistent arthritis
	1987-UA	2010-UA	2010-UA
Polyarthritis	+	+	-
ACPA positivity	+	+	+
Increased CRP	+	-	+
Increased ESR	+	-	-
Bone erosion at x-ray	+	-	-
HLA-SE	+	-	NA
Tenosynovitis at MRI	+	+	NA
Anti-Carp antibodies[a]	+	-	NA

ACPA, anticitrullinated protein antibody; +, association with outcome/increased risk; Anti-Carp, anticarbamylated protein antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-SE, HLA shared epitope alleles; MRI, magnetic resonance imaging; NA, not assessed; 1987-UA, conventional UA; -, no association/no risk factor; RA, rheumatoid arthritis; 2010-UA, contemporary UA; UA, undifferentiated arthritis.
This table summarises the risk factors described and referenced in the text. The data for HLA-SE alleles in the 2010-UA are in the Supplementary material.
[a] Predictive value is independent of ACPAs and rheumatoid factor.

predictor but can be considered of limited value because of its absence in ~95% of UA patients. An overview of 'classic' and 'novel' risk factors and their predictive ability for RA development in 1987-UA and 2010-UA is provided in Table 1.

Antimodified protein antibodies

Now that classic risk factors are less accurate or helpful, new risk factors were sought, such as newer antimodified protein antibodies (AMPAs). Anticarbamylated protein (Anti-Carp) antibodies were predictive of developing RA in 1987-UA, and that effect was independent of ACPAs and RF. In 2010-UA, however, anti-Carp antibodies were no longer predictive for the development of RA (Table 1) [19]. Anti-Carp was also rare in ACPA-negative, RF-negative UA: 2.5% of seronegative 1987-UA patients were anti-Carp positive, and only 0.01% etc of seronegative 2010-UA [19]. Antibodies against acetylated vimentin have been described [20] but, to the best of our knowledge, have not been tested in 2010-UA. Hence, multiple studies, including various AMPAs, still remain to be done in 2010-UA.

Imaging

Imaging can be more sensitive in detecting joint inflammation than physical examination of joints. Ultrasound (US) and Magnetic Resonance Imaging (MRI) were evaluated in a few studies in 2010-UA. US-detected inflammation was found predictive in 2010-UA [21,22], but regular clinical and serologic risk factors were not studied, and the added value of US remains unidentified.

A Japanese study in 2010-UA provided the first evidence that tenosynovitis detected by MRI is predictive for developing RA [23]. A large study in >400 consecutive 2010-UA patients demonstrated that MRI-detected tenosynovitis was associated with RA progression, independent of regular clinical and serological predictors (Table 1) [15]. A flowchart revealing the value of hand and foot MRI in subgroups of UA patients based on ACPA status and joint involvement revealed that MRI is most valuable in ACPA-negative UA patients with oligoarthritis; the absence of MRI-detected tenosynovitis contributed to excluding future RA development [15]. MRI was less helpful in ACPA-negative monoarthritis as the prior risk for RA was already low [15]. Follow-up research showed that an MRI of one hand is sufficient, that additional scans of the feet are not of added benefit [24], and that MRI-detected erosions are not predictive [25]. Thus, performing a hand MRI in ACPA-negative UA with oligoarthritis could aid in preventing overtreatment by identifying a group of patients that will not develop RA.

Genetics

Human leucocyte antigen (HLA)-shared epitope alleles are the strongest genetic risk factor for RA and ACPA-positive RA, in particular. While predictive in 1987-UA [26,27], the HLA-shared epitope alleles do not confer risk for RA in 2010-UA (Table 1), possibly because some of the genetic risk is already captured by the ACPA positivity.

Risk stratification models

While we have so far looked at the value of individual risk factors, a combination of factors will ultimately be required for accurate risk stratification. The so-called 'Leiden prediction model' was designed for 1987-UA and extensively validated internationally [4,5]. In addition to autoantibodies and the number of involved joints, this model contains information about morning stiffness, distribution of involved joints, symmetry, age, and gender. The idea was that with the advent of the 2010 classification criteria, which also aimed at earlier recognition of RA, this model has become redundant. Interestingly, a number of research groups evaluated the accuracy of this model in 2010-UA and found a discriminative ability that was not much inferior to what is known from the model in 1987-UA (Area under the receiver operator curve (AUC), 0.85; 0.83 in 2010-UA vs 0.87 originally in 1987-UA) [28,29]. Likewise, the evaluation of consecutive 2010-UA patients from the Leiden early arthritis cohorts revealed an AUC of 0.81 (Supplementary File S2). These data suggest that the Leiden prediction model, which is easily filled at MDCalc [30], still has some value in 2010-UA.

What is yet unexplored is whether there are variables in this model that no longer contribute to the prediction in 2010-UA and, therefore, may be omitted. Vice versa, other factors may need to be included; for instance, imaging-detected tenosynovitis may be useful to explore [15].

Finally, a crucial question is whether the development of RA is the pivotal outcome when developing risk stratification methods for UA. Alternatives include persistent arthritis or, vice versa, spontaneous remission. The latter would identify the people who should not be treated. Functional disability and loss of productivity are also of great importance. These outcomes are virtually nonexistent in prognostic research in 2010-UA.

EVIDENCE FOR THE EFFICACY OF DMARD TREATMENT FROM RESEARCH OTHER THAN PLACEBO-CONTROLLED RCTS IS LACKING

Since placebo-controlled clinical trials in 2010-UA are absent, a recent study explored the efficacy of DMARD treatment in 2010-UA using 25 years of observational data in which the inclusion period (periods between 1993 and 2019) was used as an instrumental variable for changes in treatment strategies [8]. It was hypothesised that if the use of DMARD treatment, which had increased over time, had a disease-modifying effect on UA, this resulted in lower disease activity, improved physical functioning, increased frequency of prolonged DMARD-free status, and less progression to RA. Despite the fact that DAS slightly improved in patients diagnosed from 2011 onwards (approximately −0.20 DAS units), which is related to more frequent DMARD treatment functional disability, the prevalence of prolonged DMARD-free status and progression to RA did not concomitantly improve compared with patients diagnosed from 1993 to 1997 [8]. Notably, the observed improvement in DAS28-CRP from 2011 onwards does not exceed the minimal clinically important difference of 1.0. This increased use of therapeutics without notable improvement in long-term outcomes also raises questions about benefits/risks in the treatment of UA and, as such, questions how current UA should be treated.

A possibility to gain some insight into the efficacy of DMARD treatment in 2010-UA in the short term may be to reanalyse the existing UA trials and perform posthoc analyses in which the 2010-UA patients are identified retrospectively and the treatment efficacy explored.

2010-UA IS DIFFERENT FROM PREARTHRITIS OR PRE-RA

With the recent focus on the prevention of RA, the interest in 'prearthitis' and 'pre-RA' has increased. How does 2010-UA fit

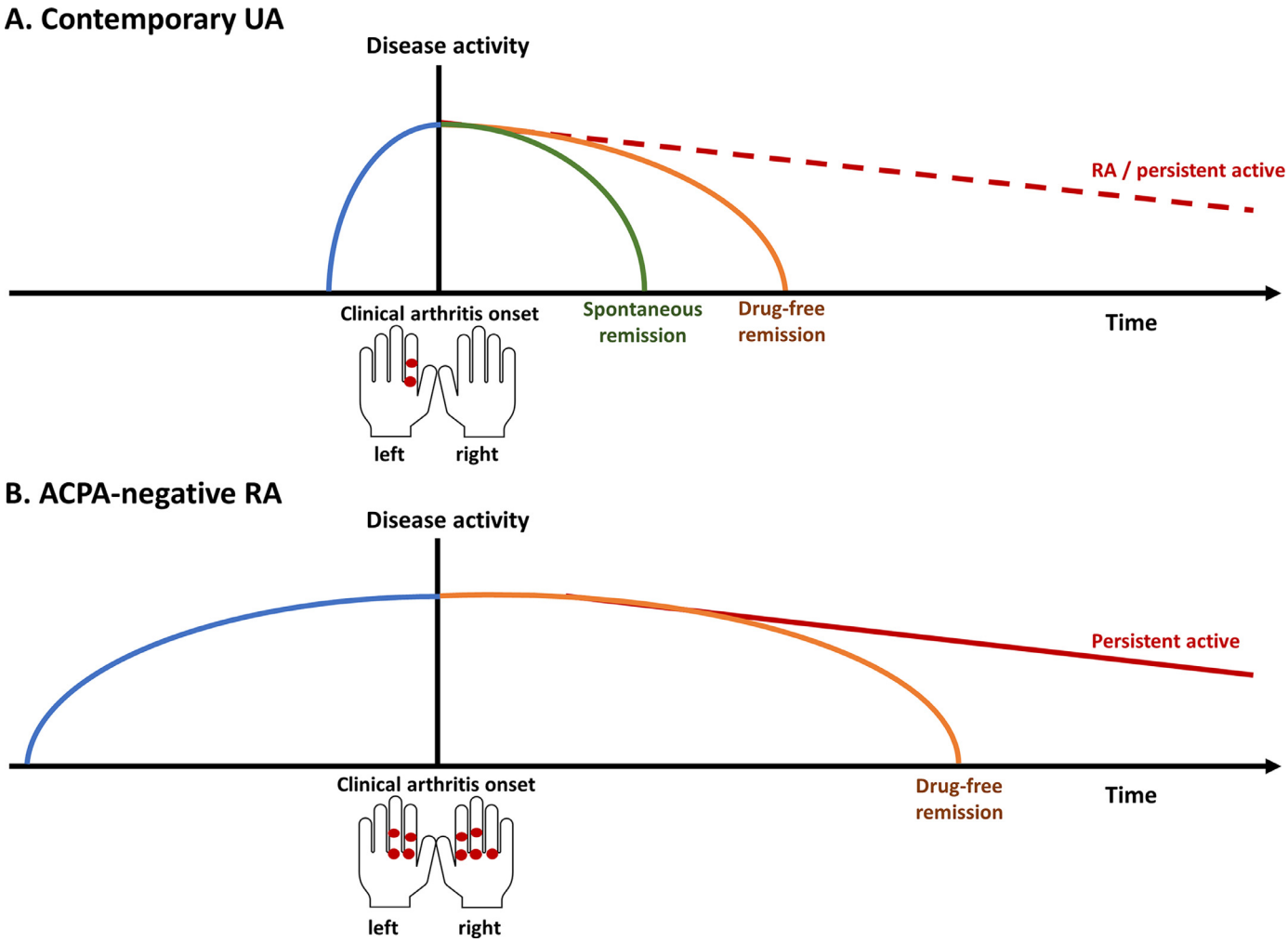

Figure 2. Conceptual differences between autoantibody-negative rheumatoid arthritis (RA) and contemporary undifferentiated arthritis (UA). Autoantibody-negative RA typically has a symptomatic prearthritic phase, presents with polyarthritis of small joints, and has a protracted disease course that may result in sustained Disease Modifying Antirheumatic Drug-free remission (DMARD-free remission) in a subset of patients. Autoantibody-negative RA also has a longer symptom duration at diagnosis than contemporary UA (median, 12-14 weeks in anticitrullinated protein antibody (ACPA)-negative RA [32,33] vs 8 weeks in contemporary UA [16]). Contemporary UA is most frequently autoantibody-negative, presents with fewer swollen joints, and regularly results in spontaneous remission or DMARD-free remission. About 10% progresses to RA. Whether UA has a symptomatic prearthritis stage is unknown. Refining the clinical and pathophysiological differences between contemporary UA and autoantibody-negative RA is part of the research agenda.

into these concepts? The crucial difference between prearthritis and UA is that clinically apparent inflammatory arthritis is, by definition, absent in prearthritis and mandatory for UA. UA has long been seen as a 'pre-RA stage' that occurs just before RA development. However, given the low frequency of 2010-UA that progresses to RA (<10%), this does not apply to the majority of UA patients. This is also supported by findings from arthralgia cohorts. Individuals at risk for RA are often identified by ACPA positivity; once clinical arthritis has developed, RA is diagnosed. Also, people with clinically suspect arthralgia generally progress directly to RA and are rarely first diagnosed with UA at the time of developing clinically apparent inflammatory arthritis [31].

2010-UA AS AN ENTITY IN THE EARLY ARTHRITIS SPECTRUM

The concepts of early arthritis and UA differ by nature; where UA is a specific category of arthritis, and the type of arthritis is unclear, early arthritis obviously refers to the time frame of the disease's onset, regardless of its specific type of arthritis.

Due to the lack of specified tools or criteria to diagnose UA, it is a less defined disease entity than other classified arthritides. Because of the often favourable disease course, an overlap with reactive arthritis could be assumed. However, the absence of obvious infectious episodes preceding autoimmunity makes this speculative. Because of ACPA negativity, an overlap with ACPA-negative RA can be considered. Some clinical characteristics at diagnosis differ between ACPA-negative 2010-UA and ACPA-negative RA at group levels: UA has a shorter symptom duration and a lower number of inflamed joints. Whether UA has a 'pre-UA period' with gradual onset of autoimmune or autoinflammatory phenomena, similar to the risk stage of arthralgia that can precede ACPA-negative RA, remains to be elucidated. Further, the disease course differs; while 2010-UA frequently achieves sustained spontaneous remission or DMARD-free remission (resembling a monocyclic course of joint inflammation), ACPA-negative RA typically has a persistent course that requires DMARD treatment, whereby part of the population can achieve sustained DMARD-free remission over time. Conceptual differences between ACPA-negative RA and 2010-UA are depicted in Figure 2 [16,32,33]. Ideally, in the future, the distinction between UA and RA will be based on differences in underlying

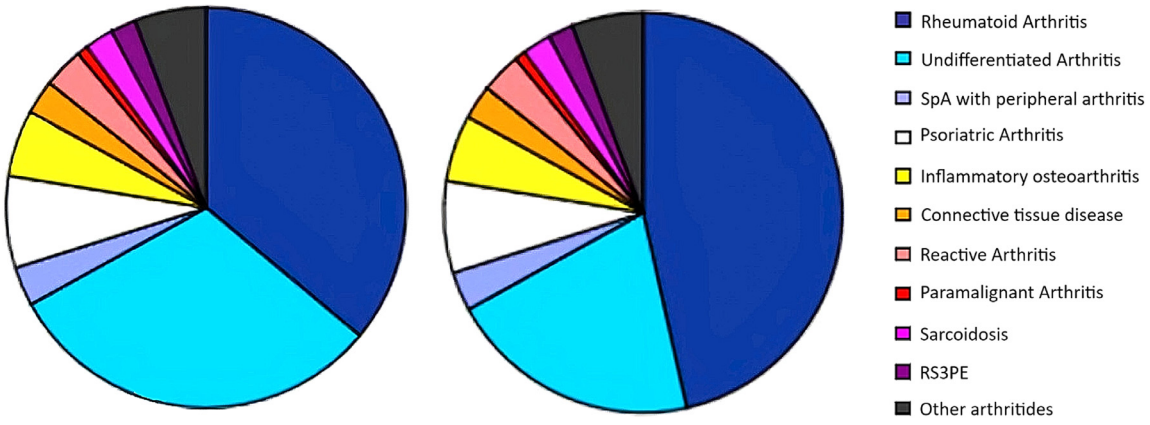

Figure 3. Distribution of diagnosis of consecutive patients with early arthritis in whom rheumatoid arthritis (RA) is defined according to the 1987 criteria (left) and the 2010 criteria (right), which has consequences for the occurrence of undifferentiated arthritis. The data are based on 4369 early arthritis patients who were consecutively included in the Leiden Early Arthritis cohort. Incident early arthritides aged ≥18 years were included, and susception of traumatic arthritis or crystal arthropathy at first presentation were exclusion criteria. Data on diagnoses were collected during the first year of follow-up. RA was defined according to the 1987 criteria (left) or 2010 criteria (right). SpA: Spondyloarthritis; RS3PE: Remitting seronegative, symmetric synovitis with pitting edema.

Table 2
Research agenda

With respect to risk stratification
• Validate the predictive value of MRI-detected tenosynovitis in 2010-UA, as well as an added value to regular clinical and serological predictors.
• Determine the added predictive value of several AMPAs in 2010-UA, in addition to regular clinical and serological predictors.
• Determine the predictive value of genetic variants in 2010-UA, also next to regular clinical and serological predictors.
• Determine the predictive value of ultrasound-detected joint inflammation in 2010-UA, in addition to regular clinical and serological predictors.
• Validation of predictors in independent cohorts from different countries.
• Develop and validate risk stratification algorithms specifically for 2010-UA by evaluating known clinical, serological, imaging, and genetic risk factors.
• Determine whether the outcome of stratification algorithms would include the persistence of arthritis, spontaneous resolution, functional disability, or work loss (rather than RA development).
With respect to the disease course
• Investigate whether 2010-UA is different from 1987-UA in the course of DAS over time and the course of functional limitations.
• Study how 2010-UA differs from 1987-UA in the ability to achieve a DMARD-free status.
With respect to understanding pathobiology
Conduct translational research at the level of systemic markers and synovial tissue:
• To understand the processes underlying 2010-UA
• To unravel heterogeneity within 2010-UA
• To discover the differences between 2010-UA and autoantibody-negative RA
With respect to differentiation/classification
• Assess whether current methods to differentiate 2010-UA from autoantibody-negative RA suffice or need to be redefined.
With respect to treatment
• Perform posthoc analyses on published trials in 1987-UA, select the 2010-UA patients, and evaluate treatment efficacy.
• Perform randomised clinical trials on 2010-UA (not only with RA development as an outcome but also disease persistence and functional disability over time).
• Determine whether methotrexate is effective as first-line DMARD in 2010-UA.
• Determine whether treat-to-target is effective in 2010-UA.
• Summarise the results of future research and update treatment recommendations for UA.

AMPA, antimodified protein antibody; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; MRI, magnetic resonance imaging; 1987-UA, conventional UA; RA, rheumatoid arthritis; 2010-UA, contemporary UA; UA, undifferentiated arthritis.

biological mechanisms, which are, however, not yet fully understood.

Therefore, despite its less well-defined definition and unknown aetiology, UA, in its contemporary form, has become an entity within the spectrum of early arthritis diagnoses. It presents as an ACPA-negative mono- or oligoarthritis and may have a less persistent disease course than several classified arthritides. Figure 3 shows the lower prevalence of 2010-UA compared with 1987-UA in the spectrum of early arthritides.

UNRAVELLING HETEROGENEITY AMONG 2010-UA

Although 2010-UA is a separate entity, heterogeneity may still exist. Unravelling heterogeneity within UA at the pathophysiological level is still impossible. Some studies have examined inflammatory cells in the systemic circulation and synovial tissue of 2010-UA and reported on differences in macrophage density or expression of monocyte-related markers in relation to the clinical outcome [34–36]. Yet, little translational research has been conducted on 2010-UA.

Alternatively, the heterogeneity at the level of clinical variables was unravelled. A unique set of 2010-UA patients, with longitudinal data collected in the era before DMARD treatment became common, were studied for the natural disease course [37]. Clusters were searched based on clinical features at initial presentation, resulting in 5 clusters differentiating patients mostly on joint involvement (3 clusters with monoarthritis, 1 with oligoarthritis, and 1 with polyarthritis). Thereafter, the clusters were evaluated by studying the disease course. The first monoarthritis cluster (18% of UA patients) had clinical arthritis of a large joint, often an acute/subacute onset of symptoms, and were more

often men. Another cluster (9%) concerned monoarthritis of the wrist; these patients were frequently obese, had rapid onset, and had no morning stiffness. The third concerned monoarthritis of a small hand or foot joint (10% of the UA population); this cluster had few characteristic clinical elements, but patients were relatively young (<50 years) and often female. The other 2 clusters were characterised by initial presentation with oligoarthritis (43% of the UA population) or polyarthritis (20% of the UA population) [37]. Patients with unfavourable outcomes (either progression to RA or having persistent disease) were hardly included in the 3 monoarthritis clusters [37]. It could be assumed that DMARD treatment would add little to these monoarthritic clusters. Follow-up research is needed to evaluate this.

CONCLUSION ON THE MANAGEMENT OF 2010-UA

All in all, the 2010-UA population is milder, both in initial presentation and in the severity of the disease course, than in 1987-UA. Today's UA population is >95% ACPA-negative, presents with mono- or oligoarthritis, frequently achieves spontaneous remission, and rarely (about 10%) progresses to RA. 2010-UA, therefore, appears to be its own patient group or entity within the spectrum of early arthritis. Research is needed on risk stratification and appropriate treatment in this patient group (see the research agenda in Table 2). It is risky that the current EULAR guidelines on the treatment of UA appear to be based on the idea that UA is largely similar to RA. Until there is more evidence that can be summarised in renewed EULAR recommendations, the treatment of 2010-UA is a matter of common sense, taking into account the risk of undertreatment and overtreatment, as well as the wishes and possible treatment goals of the patient.

Acknowledgements

Dennis Ton is acknowledged for this help in designing the figures.

Contributors

AHMvdH-vM drafted the manuscript. AHMvdH-vM and DA finalised the manuscript and approved the final version. AHMvdH-vM is the guarantor.

Funding

None.

Competing interests

None.

Patient consent for publication

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Ethics approval

Not applicable.

Data availability statement

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2025.01.036.

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