Use of methotrexate in undifferentiated arthritis

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ABSTRACT

The prognosis of patients with undifferentiated arthritis (UA) may vary from self-limited to severe destructive rheumatoid arthritis (RA). Based on the chance that these patients will develop RA and based on the safety profile of a course of methotrexate for 30–90 days, many clinicians consider using methotrexate in this patient category using the "n of 1" trial principle. During the last few years, more data on interventions in UA have become available that provide guidance in the prescription of drugs to UA patients.

Although early descriptions of RA date back to 1800, Garrod was the first to name the disease 'rheumatoid arthritis' in 1850 (1, 2). About 100 years later, the American College of Rheumatology (ACR) proposed the first classification criteria, in order to distinguish RA from other types of joint diseases.(3) In 1987 the criteria were revised, and recently the last revision has been published although the characteristics of this last modification, the 2010 criteria, are not yet fully investigated (4). The 1987 criteria have served well as inclusion criteria to select homogeneous patient groups for clinical trials, but they have been limited for possible diagnostic value, particularly with poor sensitivity for early disease.

An approach to early disease, termed "undifferentiated arthritis" or UA, has been initiated to develop prediction models for whether patients were more likely to have a self-limited process or develop progressive RA (5, 6). The newly designed 2010 criteria for RA include a weighted scoring system in which different items such as involvement of number and type of joints, serology, acute phase proteins and symptom duration each contribute to arrive at a diagnosis. (4). No trials have yet been performed with patients who were selected based on these 2010 criteria.

The new criteria redefine the disease, as the label 'RA' is actually moved towards an earlier stage. This has several consequences. It is unknown whether the sensitivity and specificity (and thus predictive value) of the new criteria will be high enough to accurately classify all patients. Moreover, the criteria lump disease subsets in which the underlying pathogenesis may differ such as ACPA-positive and ACPA-negative disease (7). Furthermore, existing data on available therapies may have less relevance in this newly defined 'RA' population, as these come from trials with patients fulfilling the 1987 ACR criteria for RA. Thus, until the value and therapeutic consequences of the new criteria for RA have been evaluated for clinical practice, UA remains the easiest concept.

Nevertheless UA is a non-validated description of a phenotype. In clinical practice all arthritis that cannot be diagnosed into one of the categories will be referred to as *e causa ignota* or as "undifferentiated". For inclusion in early arthritis cohorts, various definitions and criteria are used for the early phase of arthritis, which makes it difficult to compare directly the compositions of the different study groups. 'Early arthritis', 'early RA', and 'undifferentiated arthritis' are terms that are in use for describing either arthritis that might evolve into RA or that has been diagnosed early after onset of arthritis or even early in the disease course of definite RA. Therefore, patients with UA are in general seen as those patients with the potential for development of persistent inflammatory arthritis, including RA, but in whom a recognised clinical pattern does not (yet) exist.

Notwithstanding imperfect definitions of the phenotype for clinical practice, data on the disease course in UA are known and a considerable proportion of these patients develops RA. It is known that during this disease process a number of pathogenetic events occur, which can be prevented by rapid initia-

tion of treatment (8-10). So if one cannot arrive at a diagnosis or feels that the diagnostic process is too expensive or cumbersome, then the initiation of methotrexate therapy in an "n of 1"-trial is a reasonable choice (11). The considerations of starting low-dose MTX in this setting are the excellent safety profile of a 30–90 day trial of low dose MTX while on the other hand the most straightforward approach to arrive at a diagnosis in UA patients is observation for 3–12 months (11, 12).

This review aims to provide background of MTX treatment in patients with UA. To this end, we will review the concept of UA, the treatment trials in UA, an RCT with MTX in UA (the PROMPT)-study and discuss the evidence that the pathogenesis of ACPA-positive RA is different than ACPA-negative RA and its implications for initiating methotrexate therapy.

Undifferentiated arthritis

Patients with RA may present with typically distributed inflammatory polyarthritis, but can also have mono- or oligoarthritis, which does not (yet) fulfil criteria for any rheumatologic disorder. If no certain diagnosis can be made, this form of arthritis is called unclassified or undifferentiated arthritis (UA) (13). UA represents a variety of disorders, some self-limiting and prone to go into spontaneous remission, others potentially chronic and damaging. Follow-up data of various Early Arthritis Cohorts, set up to promote early detection and treatment of rheumatic disorders, have shown that up to 50% of UA patients have self-limiting disease, whereas 17–32% (depending on the definition of UA) eventually progress to a syndrome that fulfils the 1987 ACR classification criteria for RA (14-16). The prognosis of those patients who present with UA but progress to RA within one year is similar to that of patients who present with RA at baseline (17). Thus, a subset of UA patients is actually in an early stage of RA. Since it has become clear that starting treatment with disease modifying anti-rheumatic drugs (DMARDs) earlier leads to improved outcomes for patients with RA, starting anti-rheumatic therapy already in the UA phase might result in even more sustained benefits and potentially even a chance for cure (18-20). This has been called the 'window of opportunity' hypothesis, pointing towards a restricted timeframe where therapeutic intervention might permanently alter the disease course (21).

Randomised controlled clinical trials in UA

In a recent pilot study in ACPA-positive arthralgia patients, it was tried unsuccessfully to alter the disease course by two steroid injections (22).

A few randomised short-term intervention studies have tried to alter the course of early UA (thus arthritis instead of arthralgia). In the STIVEA trial, three weekly intramuscular methylprednisolone injections in inflammatory polyarthritis of 4–10 weeks duration postponed the need for DMARDs and resulted in a small increase in the proportion of patients that had resolved disease after 12 months. Clearly longer follow-up is needed (23). In the larger SAVE study in a similar patient population, a single 120mg intramuscular methylprednisolone injection was clearly not effective in inducing remission or delaying development of RA (24).

Based upon these data we conclude that a short-term intervention with parenteral prednisone is effective only in reducing symptoms for a short period of time but lacks the capacity for long-term disease modification.

A tapered high oral dose of prednisone has not yet been evaluated in UA.

Two other powerful antirheumatic therapies, infliximab (α TNF-blocker) and abatacept (a T-cell co-stimulation inhibitor), have been tested (25, 26) in two small studies in UA patients. Anti-TNF did not prevent progression to RA in the small pilot trial. The small trial with 6 months of abatacept was performed in ACPA-positive UA patients. After 1 year, 12 (46%) in the abatacept group fulfilled ACR criteria for RA and 14 (54%) did not. In the placebo group, 16 (67%) fulfilled the ACR criteria for RA. Although this is not statistically significant, it is intriguing that the rate of RA development is highly similar in the previously reported ACPA-positive Leiden UA group (69%) and lower than in the ACPA-positive Berlin UA group (91%), Birmingham (92%) and the Japanese data set (92%) (29). Therefore, an intervention with abatacept in ACPA-positive UA patients seems promising.

Treatment strategies

In the past decade, four important further changes have led to considerably improved treatment outcomes. First, early diagnosis and prompt initiation of DMARD therapy led to earlier suppression of disease activity with long-term impact (18-20, 29). Second, DMARD combination therapies, including those including corticosteroids, have proven superior without more toxicity than DMARD monotherapies (30-33).

'Tight-control' (frequent evaluations and adjustments of therapy with validated tools aiming at a pre-set goal of minimal disease activity), has been proven to result in better outcomes than 'routine care' (34-37). As a result of these changes, sustained disease remission has become an achievable goal of RA treatment (38). This improvement has changed the perspective for RA patients (4, 11); thus it makes sense to include these principles in UA trials as well. Indeed, tight control trials are possible in UA since the DAS has been validated in UA as well (39). With respect to the PROMPT-study indeed adaptation of the MTX dose has been done based on disease activity and as such this is the first "strategy study" in UA.

Methotrexate

Methotrexate is regarded as a cornerstone of RA treatment (4, 11). Since its first use in patients with RA in the 1960s, the efficacy and toxicity profile of methotrexate (MTX) has been well established in randomised controlled trials (RCTs) in the early 1980s and in longitudinal cohort studies in the 1990s (40-43). MTX has shown higher retention rates compared with other DMARDs in long-term observational studies, demonstrating its favourable efficacy/toxicity ratio (44, 45). In addition, MTX suppresses the progression of radiographic joint damage (46, 47). In high dosages, MTX as a folate antagonist acts anti-proliferative via blocking

purine synthesis. However, in the dosages used in RA, 7.5–30mg/wk, MTX probably has antiinflammatory and immunosuppressive (48) actions via various routes which are still being explored (49). There is large variability in how patients respond to MTX, both in terms of efficacy and toxicity. Only part of this variation can be explained with clinical markers, such as gender, baseline disease activity and RF status, but pharmacogenetic data might enhance the prediction of the response (50, 51). Multiple polymorphisms in genes encoding proteins in the MTX metabolic pathways have already been linked to either efficacy or toxicity (52).

MTX is currently recommended by the European League Against Rheumatism (EULAR) as the first DMARD of choice in the treatment of RA and as the anchor drug to which other DMARDs can be combined and new drugs can be evaluated (53, 54, 4, 12). Recently evidence-based recommendations how to use MTX have been published (55).

The PROMPT study

The effect of MTX as remission induction therapy to prevent the development of RA was investigated in the first randomised placebo-controlled trial in UA: the 'PRObable rheumatoid arthritis Methotrexate versus Placebo Treatment' (PROMPT) study (56). In the PROMPT study, 110 patients with UA fulfilling the 1958 criteria for probable RA were treated for one year with either MTX or placebo. The patients who were randomised to MTX had a delayed onset of RA, but eventually still fulfilled the 1987 RA criteria as often as patients who received placebo. Thus MTX did not prevent, but only postponed RA. Subanalyses clearly showed statistically significant differences in response to MTX treatment between patients with and without antibodies to citrullinated proteins (ACPA). The RA-postponing effect of MTX was observed only in patients with and not in patients without ACPA. The beneficial effect of MTX on symptoms, function and damage progression was statistically significant only in the ACPA-positive, but not in the ACPA-negative UA patients.

After one year MTX (or placebo) treatment, medication was tapered and discontinued in the UA patients who had not developed RA. This resulted in a flare of disease and ongoing radiographic progression, predominantly in the ACPA-positive patients. MTX therapy did not induce more drug-free remission than was observed in the placebo group and predictors for drug-free remission were similar to characteristics of self-limiting disease. These data suggest that one year MTX did not induce a long-lasting change in the disease progression from UA to RA, certainly not for ACPA-negative UA, and only to a certain extent but not enough to induce more remission for ACPA-positive patients.

ACPA-positive *versus* ACPA-negative UA

Ideally treatment choices are guided by biomarkers of the underlying pathophysiological process (4). UA is defined by clinical symptoms and will consist of several different disease subsets of which the most prominent distinction is made by the presence of ACPA. In UA one of the strongest predictors for RA is the presence of ACPA. ACPA can be present years before the disease becomes clinically apparent, are highly specific for RA and 93% of ACPA-positive patients with UA go on to develop RA within three years (56, 57). This was also shown in the PROMPT study, where almost all ACPA-positive UA patients eventually developed RA. Since also the course of ACPA-positive disease, once developed into RA, is clinically more severe and more destructive than ACPA-negative disease, it is clear that ACPA-positive UA warrants early DMARD treatment (59).

DMARD treatment of ACPA-negative UA is more controversial, since it probably represents a variety of diseases, with a different genetic background and variable disease prognosis (60, 4). With the current prediction models the risk for RA is particularly difficult to determine in ACPA-negative UA patients, as they lack one of the most important factors adding to the prediction score. Nevertheless, the burden of ACPA-negative UA can be considerable. In the PROMPT study, ACPA-negative patients presented with a similar amount of tender and swollen joints as ACPA-positive patients, 35% of them fulfilled the 1987 criteria for RA during the study and 14% had persistent UA.

Thus initiating treatment in ACPA-positive with MTX for relatively long periods is advisable; in our view discontinuation should not be done before at least a year of therapy and only be considered in the case of full clinical remission.

In patients in which MTX has been initiated following the "n=1 methodology", the choice has been made for a short-term course of 30-90 days (11). In case of a good response or remission tapering and discontinuation of MTX seems logic. In case of continuous disease activity one can hopefully arrive at a diagnosis and then follow current treatment schedules as published elsewhere (12, 4).

One major point what has not been addressed so far is that we do not know what the influence of the clinical setting (primary care, hospital care) on the test characteristics of criteria and prediction models is. From a historical perspective it was already observed in 1972 that a large proportion of the patients that fulfilled the 1958 criteria for RA when identified in a population had at evaluation 3 to 5 years later no evidence of disease (61). The completely different disease course in patients collected in different settings can be explained by the theories of Bayes. Bayes has influenced thinking on probabilities by demonstrating that the probability of disease, as estimated by a positive test result, is dependent on the prevalence of the positive test result as well as on the prevalence of the disease. Since the prevalence of the different diseases, as well as the prevalence of "test" characteristics such as duration of symptoms at first visit, arthritis in respective joints, will differ between each new patient seen by different rheumatologists and therefore the probability of the presence of disease will be different, according to Bayes' law. This fundamental problem affects the use of any set of prognostic criteria to define the group of patients with "early inflammatory polyarthritis." Classification

criteria have been instrumental for the comparison of clinical studies in different groups all over the world. However, if clinical studies differ on the basis of the context in which the inclusion of patients has taken place, the interpretation of subsequent clinical studies is difficult. As such we have to wait how large the effect of the different context will be with respect to use of the 2010 criteria and prediction models (62).

Future perspectives

A major focus of future research will be the continuing search for effective strategies that can alter the disease course of UA patients towards a milder disease, more remission or even prevention of the development of chronic destructive RA. Since it is still unclear when, for whom and how to start early DMARD treatment, new clinical trials and basic research are needed to enhance our understanding of the pathophysiological pathways leading to RA. Hopefully, this will lead to better targeting of the 'window of opportunity' at the right time, in the right patients and with the right therapy, by more precise prediction of who will develop RA.

In the future we hope to see the results from trials in recent-onset UA in which treatment strategies are being evaluated that aim to achieve clinical remission in which case tapering and discontinuation of medication follows. Such trials will demonstrate whether the hypothesis that with induction therapy RA can be prevented in the UA patients and longstanding remission or cure might be induced.

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