

Incidence of Rheumatoid Arthritis Onset in Patients with Arthralgia and Anti-Citrullinated Peptide Antibody Positivity: Pilotstudy on Effectiveness of Hydroxychloroquin Treatment

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Received date: April 15, 2016; Accepted date: May 03, 2016; Published date: May 06, 2016

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Abstract

Objective: A relevant subset of patients with ACPA-positive arthralgia will develop arthritis within one year. Hence, an ACPA-positive patient cohort with arthralgia was treated with hydroxychloroquine (HCQ) and was followed-up in terms of RA-manifestation and arthralgia complaints.

Methods: Since 2009 all patients presenting with arthralgia showing positive ACPA without clinical signs of arthritis were investigated retrospectively at a large outpatient facility in Lower Saxony, Germany. Body-weight adapted hydroxychloroquine-therapy was started at outset and assessments comprise a detailed documentation of arthralgias and rheumatological status (DAS28). The RA-onset rate within 12 months after enrollment is regarded as the primary outcome; secondary outcomes are the clinical course and humoral inflammatory activity.

Results: Within 12 months one of 24 patients developed RA (5%), one further patient within 24 months (10%). Regarding the secondary outcomes the number of arthralgic sites decreased highly significant, the DAS28-score and the rheumatoid factor improved after both 12 and 24 months follow-up ($p < 0.05$). Furthermore, the mean steroid dosage could be tapered from 5 mg to 1 mg, and to 0 mg, respectively. In contrast to the present pilot study, conventional treatment (without DMARDs) in seropositive arthralgia patients yielded about 6-fold and 3-fold higher rates of RA-incidence within 12 months and 24 months, respectively.

Conclusion: Since these results are promising, randomized controlled studies are needed to evaluate the effects of HCQ on RA-prevention in seropositive arthralgia patients and to define its role regarding the clinical course of seropositive arthralgia within a possible "window of opportunity".

keywords: Citrullinated peptide antibody; Arthralgia; Rheumatoid arthritis onset; Hydroxychloroquine; Observational study

Introduction

In the preclinical phase of rheumatoid arthritis (RA) often autoantibodies can be found [1]. In particular, the presence of antibodies to citrullinated proteins (ACPA) and/or IgM rheumatoid factor (IgM-RF) are an important risk factor for the clinical manifestation of RA with a five-year incidence of 2% in the general population [2]. Recent studies have shown the special relevance of ACPA in patients presenting with arthralgia [3]. In a clinical cohort of seropositive patients with a history of arthralgia but not arthritis (either ACPA or ACPA and IgM-RF positive), 32% developed arthritis within the following 12 months that could be classified as RA according to the 2010 American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) criteria, respectively.

The course of RA is known to have substantial consequences regarding physical aspects such as joint destruction and various comorbidities resulting in increased death rate [4], as well as

psychological and social impairments due to disabilities in activities of daily life [5]. Since radiological bone erosions and joint destruction are reported to occur already in the early stages of RA [6], early and aggressive treatment have become a prime target in RA management.

Various studies support the concept of a limited "therapeutic window of opportunity" at RA onset in which the long-term course of the disease can be altered by tailored treatment in a way that cannot be achieved outside this time frame [7]. The early treatment (e.g. within the first 3 months after symptom onset) shows to have more favourable clinical outcomes compared to treatment in later stages [8-10]. This counts also for a more aggressive treatment in this window leading to decreased radiological progression [11].

New data reported by van Nies et al. [12] suppose a non-linear relationship between reducing time to treatment and RA-symptom duration or favourable clinical outcomes with a turning point after which the benefit decreases. Accepting the concept of a "window of opportunity", the question arises as to how the starting point of this window can be defined. The van Nies study employs the time point when the patient reported the „first musculoskeletal symptom deemed relevant to the current complaint“. In this context, the patient group with ACPA-positivity and arthralgia appears to be of special interest.

According to the results of the van Nies study, arthralgia patients who develop an RA might already have missed their window of opportunity if the arthralgia phase lasted for more than six months. Since one third of the seropositive arthralgia patients are diagnosed with RA within the next 12 months, a more intensive therapy than just a symptom-related regime might be of benefit in this subgroup.

There is scarce evidence on preventive treatment options for patients with seropositive arthralgia who are at risk of developing RA. A placebo-controlled intervention study on dexamethasone has been published by Bos et al. [13] aiming at reducing autoantibody-levels and thus delaying or preventing RA onset. Although a certain effect on ACPA and IgM-RF can be detected, no significant change in the clinical course was associated (about 20% of the patients in both groups showed arthritis within 26 months). The authors suggest that further trials should either cover more aggressive immunosuppressive treatment options or a tolerogenic strategy. The current literature delivers no information on other treatment strategies that have been employed in this patient group. The present study aims therefore at investigating whether HCQ-treatment could influence the onset of arthritis or the clinical course of these arthralgia-patients.

Methods

Patients

Since 2009, all patients complaining about arthralgias showing positive ACPA without clinical signs of arthritis were considered for recruitment by chart review at a large outpatient facility in Lower Saxony, Germany. The arthralgias had to be persisting for at least 6 weeks. The ACPA tests were performed with an Anti-CCP-Elisa test from Euroimmun (Lübeck, Germany).

Excluded were patients with signs of arthritis at baseline examination, those refusing treatment with hydroxychloroquine and patients whose symptoms declined spontaneously. Patients presenting with prior DMARD treatment were not taken into account. The presence of erosions at the arthralgic sites were ruled out by standard radiological examinations taken prior to the start of the treatment.

Data capture and data processing were anonymized and carried out at the Hannover Medical School. All patients were informed about the experimental therapy and gave their informed consent.

Intervention

Treatment with body-weight adapted doses of hydroxychloroquine was started in all patients. Dosage of the medication and monitoring of side effects was carried out according to German recommendations by the "Deutsche Gesellschaft für Rheumatologie" [14]. Up to a body weight of 50 kg one tablet of Hydroxychloroquine (HCQ, 200 mg) was administered per day, between 50 kg and 65 kg one and two tablets intermittently and above 65 kg two tablets. In patients with significant overweight the ideal body weight was taken as a basis for hydroxychloroquin dosage.

Study design and outcomes

Assessment of the recruited patients comprised a detailed documentation of the arthralgia (location, intensity measured by patient-related visual analogue scale), and the rheumatological status according to the DAS28-criteria including the number of tender joints (TJC) and of swollen joints (SJC) at the outset of the study (t0).

Additionally, autoantibodies (ACPA, IgM-RF) and humoral inflammatory activity (ERS, CRP) were assessed. Follow-up visits were carried out every three months at the beginning of the study (t1-t2) and then every six months (t3 up to t7) addressing the clinical and laboratory outcomes above.

The frequency of RA-onset (including patients developing arthritis without fulfilling RA-criteria) within 12 months after enrollment (t3) is regarded as the primary outcome of the present study. Secondary outcomes are the clinical course (number of arthralgia locations, intensity of arthralgia, tender joint count) and humoral inflammatory activity (ESR, CRP).

Statistics

The data were entered and analyzed with the SPSS software version 19. Firstly, a descriptive analysis was carried out displaying median and interquartile ranges (IQR) due to the character of the distribution of the variables. Subsequently, comparative analyses of the clinical course were performed with the Wilcoxon-test for paired samples. The possibilities of not developing arthritis were calculated employing Kaplan-Meier survival analysis.

Results

Patient characteristics

Up to now, 24 patients were enrolled and the median observation period has reached 24 [12;24] months. Most of these patients are women (83%) and the median age is 50 [42;67] years. The symptom duration (presence of arthralgia) at the outset of the study is reported to cover a median of 15 [11;29] months. Of the 24 patients entering the study, 21 have reached the t3 endpoint (12 months) and 12 have reached t5 endpoint (24 months), the cut-off for the present analysis.

Primary outcome

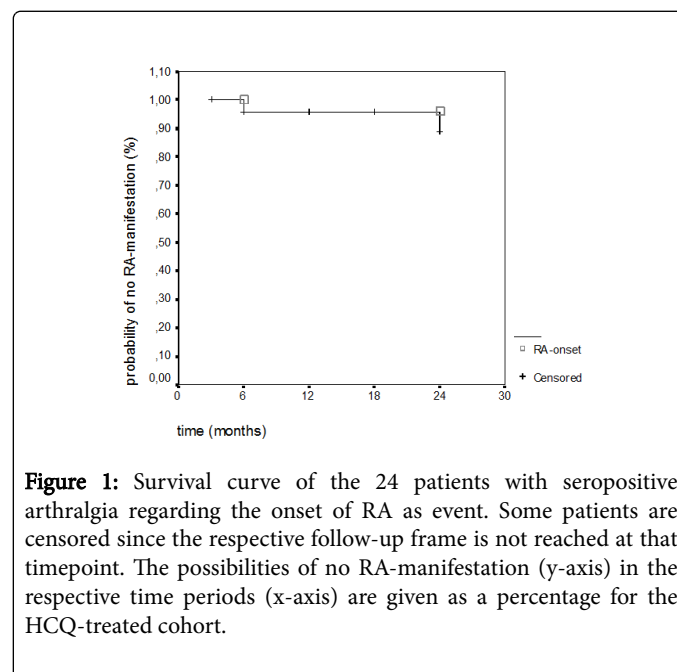


Figure 1: Survival curve of the 24 patients with seropositive arthralgia regarding the onset of RA as event. Some patients are censored since the respective follow-up frame is not reached at that timepoint. The possibilities of no RA-manifestation (y-axis) in the respective time periods (x-axis) are given as a percentage for the HCQ-treated cohort.

Of the 24 patients enrolled, only one patient (5%) developed arthritis within the following 12 months. Regarding the further follow up, an additional patient showed an RA-onset (overall RA-onset rate 10%) within 24 months. The possibility of staying in the arthralgia group and not developing arthritis is displayed as a Kaplan-Meier curve for the present sample with HCQ treatment (Figure 1).

Secondary outcomes

Clinically, patients improved after treatment with HCQ significantly in terms of the number of sites with arthralgia, and the amount of co-medication needed (Table 1). Patient rated activity and pain decreased accordingly but did not reach statistical significance.

| | Baseline (t0) (n=24) | After 12 months (t3) (n=21) | p-value | After 24 months (t5) (n=12) | p-value |
|-----------------------------------|----------------------|-----------------------------|------------|-----------------------------|------------|
| Locations with arthralgia | 3 [3.0;4.0] | 0 [0;1] | 0.0001 | 0 [0;1] | 0.003 |
| Tender joint count | 0 [0;0.75] | 0 [0;0] | n.s. | 0 [0;0] | n.s. |
| Patient-rated pain (VAS 0-10) | 5.25 [2.75;8.0] | 1 [0.25;5.25] | n.s. (0.1) | missing | n.a. |
| Patient-rated activity (VAS 0-10) | 3.5 [2.5;5.0] | 2 [1;3] | n.s. (0.1) | 1.8 [1.4;3.4] | n.s. |
| DAS28 | 2.6 [2.3;3.5] | 1.5 [1.4;2.5] | 0.04 | 1.6 [1.4;1.8] | n.s. (0.1) |
| CRP | 0 [0;0.9] | 0 [0;0.7] | n.s. | 0 [0;0.5] | n.s. |
| ESR | 14 [5;18] | 7 [4;11] | 0.05 | 9 [6;10] | n.s. (0.1) |
| RF | 149 [45;351] | 28 [0;53] | 0.001 | 16 [0;52] | 0.05 |
| ACPA | 106 [32;200] | 112 [31;200] | n.s. | 116 [34;202] | n.s. |
| Steroids | 5.0 [0;12] | 1.0 [0;5] | 0.01 | 0 [0;4] | 0.01 |

Table 1: Clinical and laboratory follow up after 12 months treatment (t3) with HCQ in patients with ACPA-positive arthralgias. Median and interquartile ranges are displayed. (n.a. =not applicable).

Highly significant was the decrease of the number of sites with arthralgia complaints from a median of three locations [3.0;4.0] initially, to a median of zero locations at present [0;1.0] ($p < 0.0001$) after 12 months of treatment, this effect can still be detected after 24 months of treatment (0 [0;1.0], $p < 0.003$).

Both patient-rated activity score (3.5 [2.5;5.0] to 2 [1;3]) and patient-rated pain score (5.25 [2.75;8.0] to 1 [0.25;5.25]) improved clinically and showed statistically a tendency to improvement ($p = 0.1$), but no significant changes, this counts also for the activity score at t5 (1.8 [1.4;3.4]) (n.s.).

The TJC decreased slightly, but since the number of tender joints was low at the beginning this reduction was not pronounced (bottom effect) (0 [0;0.75] to 0 [0;0], n.s.).

Interestingly, the level of RF decreased, as well. Prior to treatment the median level of RF was 159 IE/ml [44;355], it dropped to 27 IE/ml

[0;50] after one year of HCQ-treatment ($p = 0.003$) and to 16 [0;52] after 2 years, respectively. As to ACPA, this effect was not recorded, there was no decrease of these autoantibodies at all.

Another important effect after HCQ treatment was the reduced need for comedication regarding steroids. The daily median dosage came up to 5 mg [0;12.5] and was tapered to a median of 1 mg [0;5] ($p = 0.01$) and 0 mg [0;4] ($p = 0.01$) after 12 and 24 months, respectively.

Adverse events

Regarding the analysis of the first two years no treatment-related adverse events and no serious adverse event were recorded. Therapy with HCQ was well tolerated in all patients and there was no drop out related to treatment.

Discussion

Incidence of RA manifestation

In the present sample of ACPA positive patients presenting with arthralgia, the incidence of RA manifestation was 5% after 12 months and 10% after 24 months. There is data investigating the course of disease in ACPA-positive arthralgia patients qualifying for a comparison of these results [13,15,3].

Van de Stadt et al. [3] reported on RA incidence rates of about 32% after a median follow up of 12 months in a respective patient group, that was analyzed regarding risk factors for the development of RA. Overall, median follow-up in this cohort was 32 months [13;48], the symptom duration came up to 12 months [8;46], the mean age was 49 years, and 76% of the patients were female. Thus, symptom duration, age, and gender distribution are comparable to the present cohort. The patient sample followed by van de Stadt (2013) was not treated with DMARDs or biologicals within the observation period but received conventional care of their arthralgia [3]. In the present cohort, the patients received weight-adapted HCQ-treatment and low-dose steroid medication, that could be tapered significantly throughout the study period. Regarding the onset of RA, the incidences differ widely between these studies, with a 6-fold higher rate of RA manifestations in the DMARD naive setting after an observation period of 12 months. There are no data given for the comparison of the 24-month results in the van de Stadt (2013) cohort [3].

Rakieh et al. (2015) investigated a similar cohort of one hundred seropositive arthralgia patients [15] and found comparable results to van de Stadt et al. (2013) (3). After an observation period of 12 months 34% of the patients had developed RA and after 24 months 44%. The median follow-up period of the sample was 20 months [8;34], the mean age 51 years [24;77], 72% of the patients were female, and the mean symptom duration amounted to 23 months [8;43]. Compared to the other cohorts, the symptom duration prior to study begin is longer and might influence the incidence of arthritis manifestation on the following 12 months. No DMARDs were used prior and throughout the study. Compared to the present study, the incidences of RA-onset were 6-fold and 4-fold higher after 12 and 24 months, respectively.

The only interventional cohort published on ACPA-positive patients with arthralgia by Bos et al. (2010) is a RCT with two arms: (i) either traditional treatment without DMARD and steroids or (ii) two intramuscular injections of 100 mg dexamethasone at the outset of the study and 6 weeks later, additionally [13]. Patient characteristics of these groups were comparable to the present study and the other two

samples with a mean age of 45 and 48 years, respectively, and symptom duration of 12 months prior to enrolment. Of the overall sample by Bos et al. (2010) 64% were female; this proportion is comparably lower than in the other studies [13]. The proportion of patients developing RA after a median observation period of 26 months amounts to 20% in the untreated arm and 21% in the dexamethasone arm, respectively. The study by Bos et al. (2010) was not performed to detect differences regarding the onset of RA, but focussed primarily on the changes of autoantibody levels [13]. In comparison, the present study reports on only 10% RA-manifestation within 24 months of follow-up.

Summarizing the actual evidence on RA-incidence in seropositive arthralgia patients, the studies deliver rates of 32% and 34% [3,15] within 12 months and 20% and 44% [13,15] within 24 months after study outset. In contrast, the lower rates of 5% and 10%, respectively, in our HCQ-treated seropositive arthralgia patients might indicate a possible protective effect of HCQ.

Clinical course under HCQ treatment

The present study proposes that there is a positive clinical development in several terms regarding seropositive arthralgia patients receiving HCQ for a mean period of 24 [12;24] months. Improvements have been shown for the DAS28-score and the number of sites with arthralgia complaints, also the level of RF has decreased significantly and the steroid use could be tapered from a mean dosage of 5 mg [0;12] to 0 mg [0;4] after 24 months. There is no data available for a comparison of these clinical outcomes in seropositive arthralgia patients. This finding leads us to the assumption, that the clinical course of the persistent arthralgias is improved in these seropositive patients. Further studies are needed to investigate this assumption and the relation to the possible onset of RA.

Limitations

Overall, there is little evidence on the RA-incidence rates and the natural or the treated clinical course of seropositive arthralgia patients. The results of the present pilot study render an interesting hypothesis, that the onset of RA might be delayed or even prevented in HCQ-treated seropositive arthralgia patients. The main limitations of the data presented are related to the study design. As a retrospective cohort study, there is a moderate risk of bias that cannot be ruled out, although the clinical data assessment of arthralgia/arthritis in tertiary rheumatological care is well standardized. The sample size is quite small and further studies designed as RCTs with larger groups are needed to confirm or refute the role of HCQ in RA-manifestation.

The prevention of RA-onset by direct immune suppression has been investigated by Bos et al. (2010) applying i.m. dexamethasone[13]. The authors hypothesized that a possible reduction in autoantibodies would lead to decreased arthritis development. The results showed decreased autoantibody-levels but no effects in terms of RA-incidence. Whether this immunosuppressive treatment was not aggressive enough or other factors influenced these findings was discussed by Bos et al. [13]. Since there was a significant difference of RA-activity at arthritis onset with lower DAS28-scores in the treated group, a stronger immune suppression might perhaps have prevented arthritis. The authors propose the employment of DMARDs or biologicals as further possibly successful options.

The present pilot study focuses on the effects of HCQ, being well tolerated and known to have clinical effects in immune modulatory

therapy of RA. Since this study proposes possible effects of HCQ, further studies are needed to investigate the effects on arthritis manifestation and the clinical course of the arthralgias. Furthermore, the present results propose to broaden the possible therapeutic horizon with regard to other DMARDs.

Acknowledgement:

The study is supported by a grant from the “Deutsche Gesellschaft für Rheumatologie.”

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