Research article

Tight control of rheumatoid arthritis: Efficacy in a resource constrained setting

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Abstract

Objectives: This study was designed to evaluate the efficacy of a treatment strategy based on the "tight control" principle in patients with Rheumatoid Arthritis (RA) with a one year follow up and in a limited resource setting..

Method: This was a « before-after » observational study, comparing disease activity and handicap in the same patient throughout the year 2018 (before) and 2019 (after). This assessment was based on the « tight control » principle and performed in a rheumatology outpatient setting in patients who met the 2010 ACR/EULAR classification criteria for RA. Disease activity was assessed using DAS28-CRP, SDAI, CDAI disease activity scales and disability using the HAQ. disability index.

Results: Of the fifty patients, 47 (97%) were female and 3(6%) male. The average number of outpatient visits was 2.34 ± 1.21 with extremes of 1 and 5 in 2018 and 3.94 ± 1.6 with extremes of 1 and 8 in 2019 ($p < 0.0001$). The frequency of patients in remission before and after the tight control strategy was 4% (before) and 48% (after) respectively according to DAS28-CRP ($p<0.0001$), 2% (before) and 12% (after) according to SDAI ($p<0.0001$) and 2% (before) and 16% (after) according to CDAI ($p<0.0001$). The mean HAQ was of 1.18 ± 0.58 (before) and 0.35 ± 0.25 (after) ($p<0.0001$).

Conclusion: The "tight control" treatment strategy resulted in a significant reduction in disease activity and handicap in the majority of RA patients in a real life limited resource setting.

Key words: Tight control, Treat to target, Strategy, Treatment, Rheumatoid arthritis, Sub Saharan Africa

Introduction

Rheumatoid Arthritis (RA) is the most common chronic inflammatory disease with an estimated African population prevalence of 0.6- 1%[1]. In Burkina Faso, the hospital prevalence is estimated to be 2.84%[2]. The management of RA has evolved during the last decades to include more effective use of synthetic and biological agents combined with more effective treatment strategies[3,4]. From around 1990, the concept of "inversion of the therapeutic pyramid" was adopted into mainstream practice with the early prescription a « Disease Modifying Anti-Rheumatic Drug » (DMARD)[5,6]. In the last two decades the concept of a window of opportunity emerged[7,8] based on the early use of systematic intensive treatment with a progressive decrease of dosage (step down strategy) when stable remission is achieved[6,9]. This therapeutic strategy is based on the dual concepts of « treat to target » and « tight control ». consisting firstly in setting a goal to reach (remission or very little activity using composite indices) and secondly in scheduling regular outpatient visits « tight control » during which treatment is intensified if the goal is not reached[6]. The TICORA (Tight Control for Rheumatoid Arthritis) study was the first clinical trial to employ this strategy (Glasgow Scotland) and included 111 patients with disease duration of less than five years[10]. The patients were randomized into two groups; a "tight control" arm according to the intensified codified treatment with monthly review and the second group with a non-codified treatment and a three monthly review. The CAMERA (Computer Assisted Management for Early Rheumatoid Arthritis) study from the Netherlands

assessed two regimes in 229 patients with RA of <12 months duration. Patients were randomized to either an « intensive » methotrexate group with monthly checkups and computerized dosage adjustment (increase in dosage up to 30 mg/ week) versus a « routine » methotrexate group with 3 monthly checkups and physician based therapeutic adjustments[11]. A South African study using a tight control regimen concluded that the CDAI is the preferred disease activity index in a resource poor setting[12]. In the Democratic Republic of Congo, the mean dosage of methotrexate was found to be 9.7mg per week among 51 patients routinely followed up for 20 months[13]. In 2019 outpatient clinic was opened that solely targeted patients with chronic inflammatory diseases and especially RA patients whose treatment was based around the « Tight control » strategy. The purpose of this study was to assess, after one year, the efficacy of this strategy on the activity and the handicap of patients with RA in a country with limited resources and without access to biotherapy.

Materials and methods

Design and study population

The treatment strategy was based on the « Tight control » principle conducted in an outpatient setting comparing disease activity and functional disability in the same patient in 2018 (before), and 2019 (after). Consecutive patients with RA fulfilling the 2010 ACR/EULAR criteria were screened[14]. Fifty five were admitted to the study in 2018 and five excluded during follow up.

All patients were tested for Anti-Citrullinated Protein Antibodies (ACPA) and Rheumatoid Factor (RF). RF tested positive for values >10 IU (immuno-turbidimetric test) and ACPA positive for values >17 IU (electro-chemiluminescence with IgG capture principle). X-ray of the hands wrists and feet were routinely performed in all patients.

Intervention based on « Tight control » and study process

Patients with RA were recruited from January 2018 during their routine outpatient visit with a one year follow period. At their annual review from January 2019 onwards patients entered the «Tight control» arm of the study comprising of sequential reviews at intervals of one to three months when treatment was enhanced each time the therapeutic goal was not reached. The therapeutic objective was to reduce disease activity towards remission of the disease as defined by DAS28CRP. Haemogram, liver enzymes, urea, creatinine, blood sugar, HIV, Hepatitis B and C serologies, and chest X-rays were performed on each patient prior the onset of treatment.

Enrolled patients initially received an oral corticosteroid as bridging therapy with ‑methotrexate 15 mg/week. The dose of methotrexate was progressively increased on a monthly basis up to a maximum of 25mg/ week and supplemented with either hydroxychloroquine 400mg/day or sulfasalazine 2g/day whenever the therapeutic goal was not reached. Each checkup visit was conducted by the senior rheumatologists (TJWS, KF, ODD) assisted by the junior rheumatologists (KD, ZE,ATI).

Throughout the study period, each patient checkup included complete physical exam, pain and global disease assessment with a visual analogic scale (AVS) of 100mm and graded mild (0 -30), moderate (31-50), or severe (51-100) and rheumatoid arthritis clinical assessment

The different composite scores were calculated at each visit: DAS-28 CRP (Disease Assessment Score of 28 joints-C-reactive protein), SDAI (Simplified Disease Activity Index), CDAI (Clinical Disease Activity Index). The criteria used to define the activity of polyarthritis were those of Ahetala *et al*[15] and Smolen *et al*[16]. Handicap was assessed using the HAQ (Health Assessment Questionnaires); grading mild for scores between 0 and 1, moderate between 1.1 and 2, and severe between 2.1 and 3.

Data collection and data analysis

Data were collected using a data collection form that included socio-demographic and clinical characteristics, disease clinometry, paraclinical and therapeutic data. Data were recorded and analyzed using EPI info version 7.2.3.1 software. ANOVA test was used to compare means. Fischer test was used to compare frequencies. P-value was significant whenever inferior to 5% ($p < 0.05$).

Ethical considerations

Data were collected respectful of confidentiality. Data were collected and analyzed anonymously. Patient consent was required for the study. Study protocol conformed to ethical recommendations from Helsinki declaration.

Results

Patient characteristics: Fifty patients were enrolled in this study. Forty seven (94%) female and 3 (6%) male giving sex ratio of 0.06. The mean age was 48.42 years ± 14.74 year range 19-86 years. Fourteen (28%) had high

blood pressure and 4 (8%) had diabetes. The mean body mass index was 26.14 kg/m^2 ± 5.89 kg/m^2 range 15.6 kg/m^2 - 41.4 kg/m^2. The average duration of RA was 6.8 ± 4.68 years range 1 -18 years. Nineteen (38%) patients had at least one bone erosion. ACPA were positive in 42 patients (84%) and rheumatoid factor positive in 39 (78%) patients.

Analytic study: The average number of checkup visits was 2.34 ± 1.21 range 1 -5 in the period 2018 and 3.94 ± 1.6 range 1 -8 in 2019 (p <0.0001). In 2018 phase the majority of patients 36/50 (76%) were reviewed on 1-2 occasions compared to 39 on 3 or more occasion in the 2019 phase (Table 1).

Table 1: Distribution of RA patients according to the number of checkup visits before and after the onset of «Tight control»

Number of checkup visits	Before (2018)	After (2019)	P-value
[1-2]	36 (72%)	11 (22%)	
[3-4]	9 (18%)	22 (44%)	<0.0001
≥5	(10%)	17 (34%)	

Individual disease activity scores show improvement across all three composite scores and HAQ scores show a higher proportion in the mild category during the tight control phase (Table 2).

Table 2: Distribution of RA patients according to clinical assessment before and after the onset of «Tight control»

		Before (2018)	After (2019)	P-value
DAS 28 CRP*				
	Remission	2(4%)	24(48%)	<0.0001
	Mild activity	5(10%)	18(36%)	
	Moderate activity	36(72%)	8(16%)	
	Severe activity	7(14%)	0(0%)	
SDAI**				
	Remission	1(2%)	6(12%)	<0.0001
	Mild activity	2(4%)	28(56%)	
	Moderate activity	33(66%)	16(32%)	
	Severe activity	14(28%)	0(0%)	
CDAI***				
	Remission	1(2%)	8(16%)	<0.0001
	Mild activity	4(8%)	26(52%)	
	Moderate activity	31(62%)	14(28%)	
	Severe activity	14(28%)	2(4%)	
HAQ****				
	Absence of handicap	0 (0%)	4 (8%)	
	Mild handicap	24 (48%)	46 (92%)	
	Moderate handicap	21 (42%)	0(0%)	
	Severe handicap	5 (10%)	0 (0%)	<0.0001

*DAS-28 CRP: *Disease Assessment Score of 28 joints-C-reactive protein*

SDAI: Simplified *Disease Activity Index**CDAI: *Clinical Disease Activity Index*

****HAQ: Health *Assessment Questionnaires*

Table 3 shows the reduction in tender and swollen joints patient and physician pain scores, mean DAS28-CRP 3.94-2.60 (p<0.0001); SDAI 21.03 -9.06 (p <0.0001); CDAI 19.43-8.55 (p<0.0001).and HAQ 1.18 - 0.35 (p<0.0001). Treatment regimes are tabulated showing a significant reduction in corticosteroid dosage between the two regimes.

Table 3: Summary of the mean values of several items

	Before (2018)	After (2019)	Probability
Mean NJP	6.97± 5.73	2.38±2.69	< 0.0001
Mean NJS	1.30 ± 1.73	0.44 ± 0.81	0.0019
Mean EVA patients	51.20±15.94	27.34±12.84	<0.0001
Mean EVA physician	50.12±14.5	25.72±11	<0.0001
Mean DAS28-CRP	3.94 ± 0.90	2.6 ± 0.72	<0.0001
Mean SDAI	21.03 ± 9.97	9.06±5.47	<0.0001
Mean CDAI	19.43 ± 9.55	8.55±5.85	<0.0001
Corticotherapy	33 (66%)	10 (20%)	<0.0001
Mean dosage (mg/day)	12.61±19.95	3.28 ±14.29	0.0084
Methotrexate	43 (86%)	49 (98%)	0.0297
Mean dosage (mg/week)	15.99±2.84	16.28±2.98	0.6387
Combination*	3(6%)	7(14%)	<0.0001

NJP: Number of painful joints. NJS: Number of swollen joints. EVA: Pain intensity assessed through visual analogic scale of 100. DAS-28 CRP: Disease Assessment Score of 28 joints-C-reactive protein. SDAI: Simplified Disease Activity Index. CDAI: Clinical Disease Activity Index

*Association of methotrexate-hydroxychloroquine or methotrexate-sulfasalazine.

Discussion

This study was designed to evaluate the efficacy of a "tight control" regime in the treatment of RA over a period of one year. The results show a clear increase in the proportion of those achieving a reduction in disease activity Also there was a significant increase in the proportion of those achieving remission ranging from 12% to 48% in 2019 versus 2% to 4% in 2018 depending of which activity score was in use (DAS 28 CRP, SDAI or CDAI). However, any form of interpretation should take into account the study limits eg the small sample size. Moreover, the scheme of our « before-after » study could be biased. For instance, the difference between the « before » and the « after » groups could be due to the spontaneous reduction in disease activity. The patient who stands as its own control could reduce this bias. The general characteristics of our study population were similar to previous studies conducted in Burkina Faso and other sub- Saharan countries[6-22].

The onset of « tight control » significantly increased the number of outpatient visits; thus at least five checkup visits were reported in 10% of patients in 2018 and 34% in 2019 (p<0.0001). The average number of outpatient visits was 3.94, close to 4 (giving one visit every three months). This increase in the number of visits allowed physicians to see their patients more frequently and make therapeutic adjustments. In the TICORA clinical trial, patients in the « intensive group » arm were seen monthly with those in the « routine group » arm were seen every trimester[10].

The average number of painful joints (Mean NJP) was 2.38 ± 2.69 in 2019 versus 6.97 ± 5.73 in 2018 giving a reduction of 34.15%. Hodkinson *et al*[12] in a study from Soweto (South Africa) of 102 mainly, black patients reported a similar decrease in the number of swollen joints (NJS) after one year of follow up according to « tight control » strategy..

According to DAS28-CRP, about one patient out of two (48%) were in remission under the « tight control » strategy in 2019, compared to one out of twenty-five (4%) in 2018 during routine checkups. Moreover, the activity of rheumatoid arthritis was mild in eighteen patients (36%) in 2019 compared to five (10%) in 2018. Our study results were similar to those of Grigor *et al*[10] who reported, after 18 months of the TICORA study, 65% of patients in remission within to « tight control » group versus 16% in the routine. In our study, the mean SDAI went from 21.03 in 2018 to 9.06 in 2019. Thirty-four (68%) patients in 2019 had mild disease activity or were in remission compared to three (6%) patients in 2018. In a similar way, the CDAI,19.43 in 2018 fell to 8.55 in 2019. This score is valuable in sub-Saharan Africa since CRP is not readily available in all countries[12].

The « tight control » strategy contributed to improving the patient disability with a higher proportion of mild handicap in 2019 compared to 2018. According to HAQ Hodkinson *et al*[12] and Grigor *et al*[10] (TICORA)) reported similar results.

The improvement in disease activity also allowed the reduction and cessation of corticotherapy which is known as risk factor for infection and cardiovascular diseases, and overall increased mortality associated with RA[23]. Moreover, controlling disease activity also reduces the risk of RA associated osteoporosis[24].

Finally, the introduction of specific checkup visits focusing on management based on « tight control » of chronic inflammatory arthritis in general has allowed us to follow most of the recommendations of the French Society of Rheumatology regarding the management of rheumatoid arthritis[25].

Conclusion

This study demonstrates that in an African country with limited resources, the « tight control » strategy is an efficient feasible and beneficial real life approach to the management of RA by allowing physicians to reach treatment goals according to international recommendations regarding the management of rheumatoid arthritis in places where biotherapy is not financially accessible. The strategy also induced a drastic decrease of corticosteroid use which helps avoid additional cardiovascular risk through atherosclerosis or diabetes mellitus.

Declarations

Ethical approval and consent to participate: The experimental protocol was established in accordance with the ethical standards and with the Declaration of Helsinki.

Consent for publication: This was given by the participants.

Availability of data and material: Yes

Competing interests: None to declare.

Funding: None was obtained.

Acknowledgement

We acknowledge Patrick Durez for reading and correcting this manuscript.

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