ORIGINAL ARTICLE

Tight control early rheumatoid arthritis clinic in Hong Kong: a pilot study

Kitty Y Kwok 郭 殷
MH Leung 梁滿濠

Objective To evaluate disease activity in early rheumatoid arthritis patients in daily practice 1 year after applying a tight control treatment strategy aimed at lowering disease activity (Disease Activity Score 28, ≤3.2).

Design Single-arm open trial with historical controls.

Setting Regional hospital, Hong Kong.

Patients All new rheumatoid arthritis patients (onset <2 years) attending the tight control clinic from October 2008 to October 2009 were recruited. All the patients were followed up every 3 to 6 weeks and clinically assessed using the Disease Activity Score 28. Disease-modifying agent treatment was stepped up according to a preset protocol ladder and patient tolerance. The treatment target was to achieve a Disease Activity Score 28 of 3.2 or below (low disease activity). These patients were compared to matched historical controls in the rheumatology clinic.

Results Twenty patients in the tight control early rheumatoid arthritis clinic were recruited. Their disease activities were brought into better control than historical control patients who were followed up every 12 weeks. At week 52, clinical variables showed greater improvements in the intensive care group; respective mean scores (based on the Disease Activity Score 28 system) were 2.7 versus 4.2 (P<0.001); respective mean Health Assessment Questionnaire scores were 0.2 versus 1.3 (P<0.001).

Conclusion Outcomes of patients attending our locally adapted tight control clinic were consistent with previous reports in the literature. The clinic reduced rheumatoid arthritis activity faster and better. It entailed more frequent follow-up and monitoring, however. To address this strategy more objectively, a randomised trial with parallel controls is necessary.

New knowledge added by this study

- This study confirms that the tight control approach of disease activity in rheumatoid arthritis (RA) can achieve better clinical and functional outcomes in our locality.

Implications for clinical practice or policy

- Close monitoring and a protocol-driven approach to RA assessment and treatment is advocated.
- The treat-to-target approach should aim at remission and minimisation of radiological damage as long-term goals.

Key words
Antirheumatic agents; Arthritis, rheumatoid; Drug therapy, combination; Early diagnosis; Prognosis

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Department of Medicine, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong
KY Kwok, MB, ChB, FHKAM (Medicine)
MH Leung, MSc, FHKAM (Medicine)

Correspondence to: Dr KY Kwok
Email: kittykwokyan@gmail.com

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by joint inflammation and destruction.[1] The disease affects around 1% of the population and despite increasing knowledge about ideal treatment, it still confers immense physical, social, and economic cost burdens.[2] Worldwide literature shows that intensive management of RA can substantially reduce disease activity, radiographic disease progression, and deterioration of physical function and quality of life. Early assessment and close monitoring of RA patients could optimise treatment outcomes.

The treatment approach to early RA can be divided into two streams. One was adopted in the BeSt study,[3] using potent combination therapy or biological agents at the disease onset so as to achieve low disease activity or remission. Another was the tight control

approach, which was proven effective in TICORA study.[4] The latter study proved that intensive early out-patient management could improve outcomes of RA patients compared to those receiving routine out-patient care.

The aim of this study was to explore the tight control treatment protocol with respect to outcomes for early RA in Chinese patients attending a Hong Kong hospital.

Methods

This was a single-centre prospective study on patients with early RA conducted at Queen Elizabeth Hospital (QEH). From October 2008 to October 2009, all patients diagnosed to have RA in the last 2 years who were followed up in QEH with active disease activity were recruited. Disease activity was assessed based on the Disease Activity Score 28 (DAS28) that takes account of swollen joint counts (SJC), tender joint counts (TJC), patient global assessment (PGA), and inflammatory markers. Active RA disease was inferred if the score obtained for the aforementioned objective measurements was >3.2.[5] After assessment during each clinic visit, treatment was adjusted according to the protocol adopted from a tight control RA study conducted overseas (Fig 1).[4] The follow-up period of each patient was 1 year.

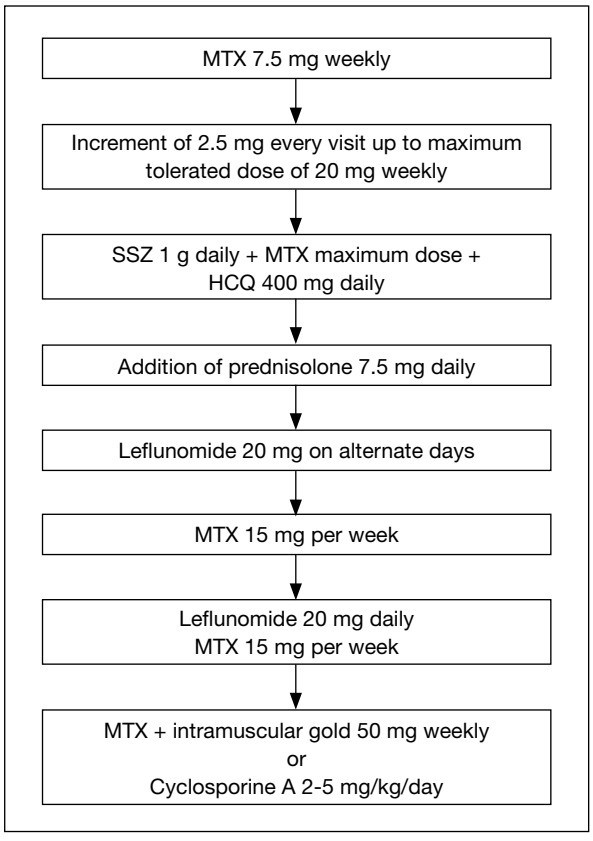

FIG 1. Protocol adopted for this study
MTX denotes methotrexate, SSZ sulphasalazine, and HCQ hydroxychloroquine

香港的早期類風濕性關節炎「嚴格控制」診所：先導研究

目的 針對類風濕性關節炎活動度的「嚴格控制」策略主要為維持病人低疾病活動度，即28處關節疾病活動度積分（DAS28）為3.2或以下。本研究評估實施「嚴格控制」策略一年後，類風濕性關節炎患者日常的疾病活動度。

設計 有歷史對照的單組開放式研究。

安排 香港一所分區醫院。

患者 於2008年10月至2009年10月期間，所有到「嚴格控制」診所的類風濕性關節炎患者都被納入研究範圍。他們的患病期均少於兩年，並會接受每三至六個星期的密切跟進，以及根據DAS28評估患者的臨床表現。按預先的協議和患者接受程度，有需要時會使用抗風濕用藥。治療目標為DAS28積分3.2或以下（即維持低疾病活動度）。最後會將本研究的病人與一般類風濕病診所中相配的歷史對照組作比較。

結果 經過12個星期的跟進後，與對照組比較，「嚴格控制」診所的早期類風濕性關節炎的20名患者有較佳的病程控制。進入第52個星期時，「嚴格控制」組在以下兩方面有明顯改善：DAS28積分為2.7（比對照組4.2），P<0.001；健康評估問卷評分為0.2（比對照組1.3），P<0.001。

結論 這個根據本地情況而改編的研究確認了過往文獻中的結果，即「嚴格控制」診所能更快及更有效減少類風濕性關節炎活動度，但同時間需要更多的跟進及監察工作。進行有相應對照組的隨機研究可客觀評估這「嚴格控制」策略的效用。

Patients who had concurrent liver, renal, or haematological disease (alanine transferase >80 IU/L, alkaline phosphatase >200 IU/L, creatinine >200 μmol/L, white cell count <4.0 x 10^9 /L, and platelet count <100 x 10^9 /L) were excluded from the study. Patients who had alcohol or drug abuse, were pregnant, or wished to conceive during the study period were also excluded.

Outcome measures

Primary outcome measures were the DAS28 at week 52 and the proportion of patients with a good response (European League Against Rheumatism [EULAR] definition: DAS28 <3.2 and a decrease in score from baseline by >1.2).[6] At 1-year post-enrolment, secondary outcome measures were the proportion of patients in remission (DAS28 <2.6), and other American College of Rheumatology (ACR) response domains including: PGA score, number of tender and swollen joints, health assessment questionnaire

(HAQ) score on daily activities function, and inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]).[7]

Intensive care group

Each patient in this group was followed up every 3 to 6 weeks. During each visit, DAS28, inflammatory indices, and HAQ scores were charted. If the DAS28 was >3.2, disease-modifying anti-rheumatic drug (DMARD) treatment was escalated according to the protocol ladder. Methotrexate (MTX) was started as first-line therapy in the protocol ladder as the anchor drug. For hepatitis B carriers, MTX was replaced with sulphasalazine (SSZ) as the first-line agent. The assessment was based on the DAS28 (an objective measure of disease activity used in studies worldwide)[8] and performed by physicians in the rheumatology team.

Historical control group

An equal number of historical controls were selected by reviewing clinical records of patients in the QEH rheumatology clinic since 2003 for whom DAS28 were available. The inclusion criteria were the same as for the intensive care group with DAS28 of >3.2. Before October 2008, such patients received usual treatment by physicians in the QEH rheumatology clinic with follow-up every 10 to 16 weeks. There was no standard treatment protocol for these historical controls, who were followed up in separate clinics with an overlap of attending rheumatologists.

Step-down protocol

If the DAS28 of the patient remained ≤3.2 for a half year, the treatment regimen was stepped down according to the protocol ladder until only one disease-modifying agent was used for maintenance, in which case follow-up became less frequent (up to every 12 weeks).

Statistical analyses

The statistical software SPSS (version 13.0, Inc., Chicago [IL], US) was used to perform the analyses. All clinical variables in the two groups were compared using the Mann-Whitney *U* test. A P value of less than 0.05 (two-sided) was considered to be statistically significant. Continuous data were expressed as mean ± standard deviation, and categorical data as percentages.

Results

From October 2008 to October 2009, 20 patients entered the intensive care group; none were excluded. Baseline characteristics and measures of activity in the two groups were similar (Table 1). Differences in baseline disease activity measures were not statistically significant. Use of DMARDs in these groups at weeks 0 and 52 is shown in Table 2.

At entry into the study (Table 2), the mean MTX dose was approximately 10 mg/week for both the intensive care and historical control groups. The majority of our patients were started on MTX as the first-line DMARD. Only one patient in the intensive care group was started on SSZ, because he was a hepatitis B carrier lest he had a hepatitis flare after MTX use. At baseline, more patients among controls were receiving steroids, which was due to their higher disease activity and less aggressive DMARD step-up therapy that was practised. No patients in the historical control group were hepatitis B carriers.

At week 52, the mean dose of MTX was 13.0 mg/week for the intensive care group versus 11.3 mg/week for the historical controls. The maximum tolerated dose of MTX in both groups was 20 mg/week. More patients were on SSZ and oral prednisolone in the historical controls. Only one patient in each group had intra-articular steroid injections for symptom control. Most patients declined intra-articular steroid injection when the option was offered. None of the patients received cyclosporine A in the intensive care group. At week 52, only one patient in the

TABLE 1. Baseline and laboratory parameters

Parameter*	Intensive care group (n=20)†	Historical control group (n=20)†	P value§
No. of women	15 (75%)	18 (90%)	0.28
No. of smokers	3 (15%)	4 (20%)	0.68
Mean (range) age (years)	46.9 (22-70)	51.8 (34-74)	0.28
Mean (range) disease duration (months)	9.0 (1-24)	9.5 (1-24)	0.68
ESR (mm/h)	59.7	55.6	0.74
CRP (g/L)	29.7	25.8	0.91
Early morning stiffness (mins)	60.5	71.0	0.22
Swollen joint counts‡	3.2	5.8	0.09
Tender joint counts‡	3.8	5.4	0.35
PGA (mm)‡	51.5	61.0	0.15
Rheumatoid factor (% positive)	15 (75%)	12 (60%)	0.32
ANA	10 (50%)	6 (30%)	0.20
HAQ‡	0.9	1.1	0.12
DAS28 (ESR)	4.9	5.3	0.25
DAS28 (CRP)	4.1	4.4	0.75

* ESR denotes erythrocyte sedimentation rate, CRP C-reactive protein, PGA patient global assessment, ANA anti-nuclear antibody, HAQ health assessment questionnaire score, and DAS28 Disease Activity Score 28

† Values expressed as mean for continuous data and No. (%) for categorical data

‡ No. of swollen and tender joints (0-28), PGA scales (0-100 mm, with higher scores indicating worse status), functional ability HAQ (0-3, with 3 the worst score)

§ Mann-Whitney *U* test

historical control group had undergone step-up DMARD therapy to cyclosporine A (Table 2). More patients among the historical controls received triple therapy (MTX + SSZ + hydroxychloroquine [HCQ]) for symptom control. The use of SSZ and prednisolone was disproportionately higher in the historical controls, both at baseline and week 52. It appeared that to maintain fair disease activity, weaning off steroids or DMARD therapy was less likely in historical controls than in the tight control group.

At week 52, all clinical variables showed greater improvements in the intensive care group than in the historical controls (Table 3). The respective mean DAS28 at week 52 were 2.7 versus 4.2 (P<0.001) and the mean HAQ scores were 0.2 versus 1.3 (P<0.001).

At the 52-week assessment, patients in the intensive care group had higher rates than controls for favourable EULAR responses (DAS28 decreased by 1.2): 14 (70%) versus 7 (35%), and remissions (DAS28 <2.6): 8 (44%) versus 0 (0%). Three (17%) of the intensive care group and nine (45%) of the historical controls achieved EULAR moderate responses (DAS28 decreased by 0.6).

Figure 2 shows the reduction in DAS28 in both groups during the study; the difference between them was sustained throughout the trial. Patients in the intensive care group enjoyed significantly greater improvements in disease activity variables (ESR, CRP, SJC, TJC, early morning stiffness, and PGA) and physical function (HAQ) [Fig 3].

Of the 20 patients in the intensive care group, five (25%) had erosive disease documented in plain radiographs at the beginning of the study, compared to seven out of 20 historical controls; one in the latter group developed erosions during follow-up.

Adverse events

In the intensive care group, two (10%) of the patients developed infections; one had a prolonged upper respiratory tract infection and the other had cytomegalovirus (CMV) infection. The patient with CMV infection presented with fever, lymphadenopathy and hepatosplenomegaly and a serum positive for CMV immunoglobulin M antibody; his MTX was stopped. Two others (10%) developed transient rashes that resolved after cessation of DMARDs. None endured Stevens-Johnson syndrome or anaphylaxis associated with DMARD use, but seven (35%) had deranged liver function after starting of DMARDs, which all normalised after stepping down the dosage, and one stopped MTX and switched to another DMARD. No patient had fulminant liver failure or dropped out of the study.

Among historical controls, three (15%) patients had upper respiratory tract infections, and two (10%) developed a rash while on DMARD therapy, and four (20%) out of 20 had mild derangement of

TABLE 2. Use of disease-modifying anti-rheumatic drug at baseline and at week 52

Drug used	Intensive care group (n=20)	Historical control group (n=20)
At baseline		
Methotrexate	19 (95%)	14 (70%)
Mean dose (mg/week)	10.1	9.6
Sulphasalazine	3 (15%)	7 (35%)
Mean dose (g)	1.7	1.6
Hydroxychloroquine	3 (15%)	4 (20%)
Mean dose (mg)	333.3	350.0
Prednisolone	2 (10%)	8 (40%)
Mean dose (mg)	7.5	6.8
Intra-articular steroid (depomedrol)	0	0
At week 52		
Methotrexate	18 (90%)	20 (100%)
Mean dose (mg/week)	13.0	11.3
Sulphasalazine	3 (15%)	9 (45%)
Mean dose (g)	1.3	1.5
Hydroxychloroquine	7 (35%)	8 (40%)
Mean dose (mg)	257.1	300.0
Prednisolone	2 (10%)	5 (25%)
Mean dose (mg)	1.8	5.4
Leflunomide	2 (10%)	2 (10%)
Mean dose (mg)	9.5	15.0
Cyclosporine A	0	1 (5%)
Mean dose (mg)	0	75.0
Intra-articular steroid (depomedrol)	1 (5%)	1 (5%)
Monotherapy	8 (40%)	3 (15%)
Triple therapy*	2 (10%)	5 (25%)

* Methotrexate + sulphasalazine + hydroxychloroquine

TABLE 3. Results for clinical variables at week 52

Clinical variable*	Mean (range)		P value†
	Intensive care group (n=20)	Historical control group (n=20)	
ESR (mm/h)	25.3 (9-45)	52.3 (9-130)	0.009
CRP (g/L)	3.7 (0.2-15.9)	19.8 (0.3-120)	0.002
Early morning stiffness (min)	2.33	22.00	0.003
Swollen joint counts	0.2 (0-2)	1.6 (0-13)	0.033
Tender joint counts	0.6 (0-3)	2.2 (0-6)	0.002
PGA (mm)	19.4 (0-40)	45.5 (20-90)	<0.001
HAQ	0.2 (0-0.9)	1.3 (0-1.6)	<0.001
DAS28 (ESR)	2.7 (1.6-3.8)	4.2 (3.2-5.4)	<0.001
DAS28 (CRP)	2.0 (1.3-2.9)	3.4 (2.2-4.7)	<0.001

* ESR denotes erythrocyte sedimentation rate, CRP C-reactive protein, PGA patient global assessment, HAQ health assessment questionnaire score, and DAS28 Disease Activity Score 28

† Mann-Whitney *U* test

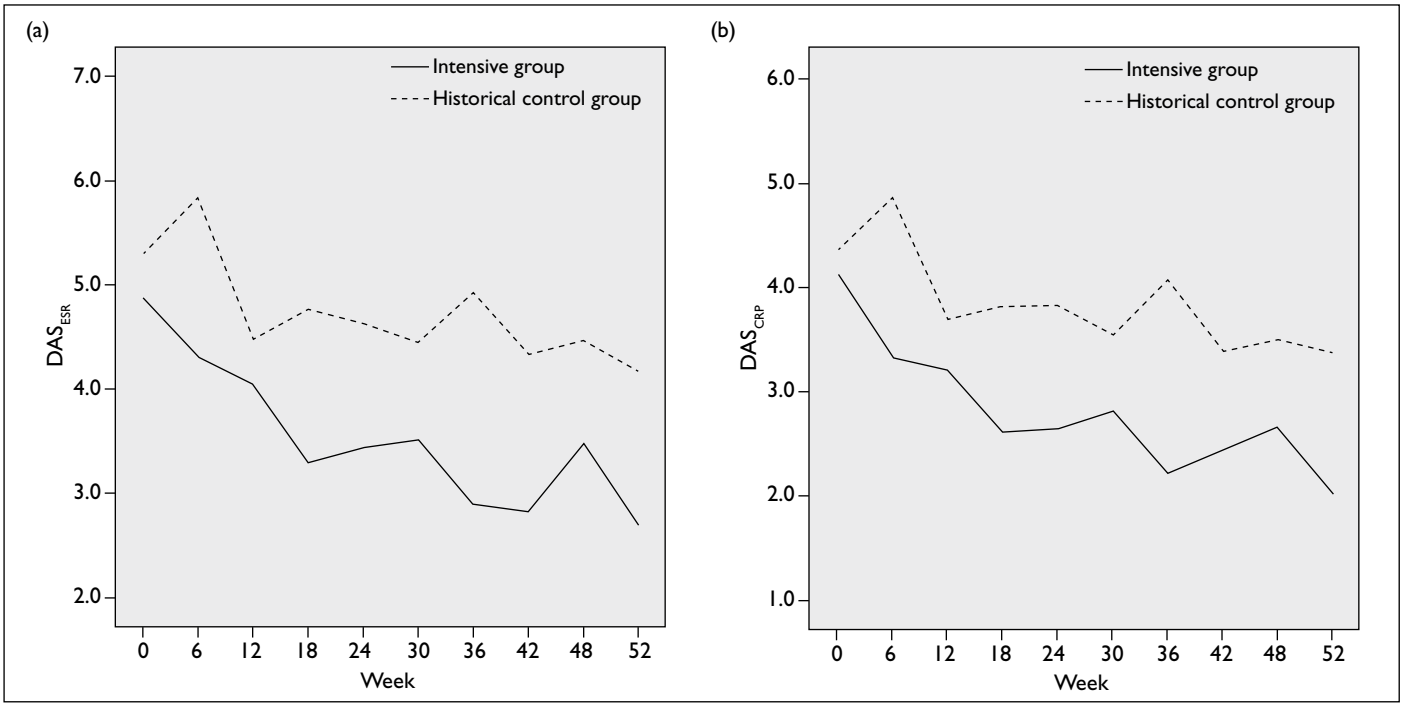

FIG 2. Mean disease activity score for (a) DAS28 ESR, and (b) DAS28 CRP over time for intensive care and historical control groups
DAS28 denotes Disease Activity Score 28, ESR erythrocyte sedimentation rate, and CRP C-reactive protein

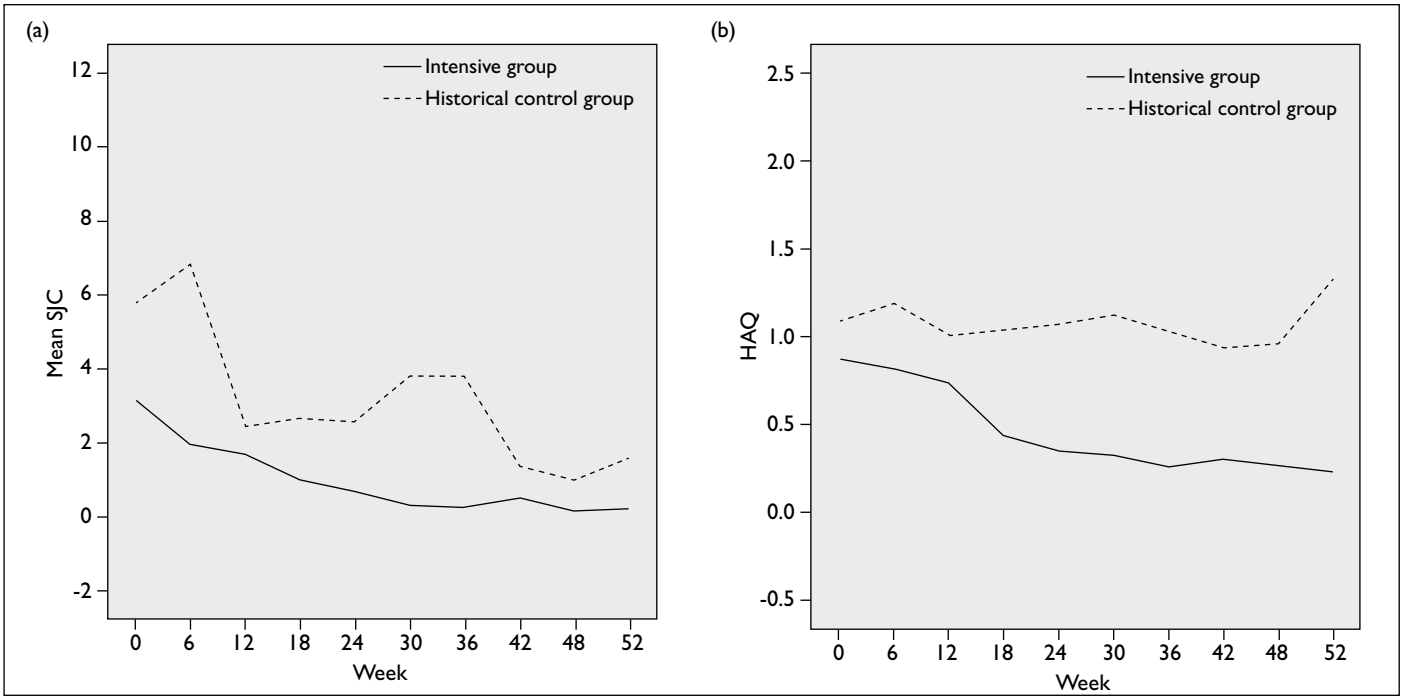

FIG 3. (a) Swollen joint counts (SJC) and (b) functional disability (health assessment questionnaire [HAQ] score) over time for intensive care and historical control groups

liver function, which normalised after switching the DMARD. Other adverse effects in the historical controls were malaise and alopecia (both attributed to MTX), dyspepsia (attributed to MTX and HCQ), blurred vision and maculopathy (both attributed to HCQ), vomiting (attributed to SSZ) and diarrhoea (attributed to leflunomide). There was no significant morbidity or mortality in this group.

Discussion

Having entered the era of treat-to-target for

management of early RA, ours was a locally adapted pilot study to assess a tight control treatment strategy for early disease. It was proven that protocol-driven treatment could achieve good clinical responses. In these studies (TICORA,[4] BeSt,[3] FIN-RACo,[9] and CAMERA[10]), a predefined treatment goal was set. In our pilot study, we showed that more frequent follow-up (3-6 weeks) and monitoring of RA disease activity and step-up therapy according to a protocol could achieve favourable disease activity (as measured by DAS28 responses). Moreover, our treatment target was low disease activity, ie DAS28 of ≤3.2. With earlier diagnosis of RA based on the EULAR/ACR 2010 classification criteria[11] and by adhering to a protocol-driven approach, nowadays remission is a realistic goal. We also demonstrated better function (HAQ) scores in the intensive care group compared to the historical controls. Studies also showed that earlier and aggressive treatment achieves better radiological outcomes, including less erosions and less joint destruction.[3]

The TICORA study[4] applied the tight control approach to treating RA patients with a history of less than 5 years. In all, 111 patients were managed in the two arms; intensive care group patients were followed up 6-weekly and the historical controls every 3 months. The treatment protocol was DAS-driven. A significant mean decrease in DAS was evident in the intensive care group (-3.5 vs -1.9), in which 65% of the patients achieved remission. In our pilot study, 70% (n=14) of the intensive care patients achieved a good DAS response (DAS28 ≤3.2) versus 35% (n=7) in the controls, whilst corresponding remission rates were 44% (8 patients with DAS28 <2.6) versus none among historical controls.

Our treatment protocol entailed early combination therapy if patients were not able to achieve good disease activity after maximisation of MTX therapy (as the anchor drug for RA). The BeSt study[3] in the Netherlands showed that initial combination or initial biological therapy achieved better disease activity scores of 71% and 74%, respectively, compared to sequential monotherapy or step-up combination treatment approaches.

With a relatively short 1 year of study period, the number of clinic visits in the intensive care group was greater than that in the historical controls, which increased the chance of step-up therapy in the former group. A longer study period is nevertheless warranted.

Our data for historical controls were collected retrospectively, while the data were prospective in the tight control clinic. Thus, our pilot study was a single-arm intervention with no randomisation. Moreover, the sample size was relatively small (20 new early RA patients included in 1 year). These limitations could be addressed in future larger-scale, randomised and longer follow-up studies. The small sample size did not permit multivariate analyses to assess possible confounding. Another limitation was that the assessment of DAS28 was performed by physicians in the rheumatology team who were not blinded.

In May 2010, the EULAR published a treatment algorithm[12] for RA. It stratified RA patients to enable a more aggressive treatment pathway if they had a poor prognosis (high titres of rheumatoid factor and anti–cyclic citrullinated peptide levels, very high disease activity on presentation and early erosive disease).

Our protocol was designed to examine the efficacy of the tight control treatment approach. Therefore we did not include biological therapy in the protocol. Worldwide studies have shown that early biological DMARD use (eg anti–tumour necrosis factor therapy) can achieve better control of disease activity and better radiological outcomes. In the open Swefot trial from Sweden,[13] despite a good clinical response on MTX therapy, there was radiographic progression. Another 2-year radiographic follow-up from the TEAR study[14] showed that a higher proportion achieved radiographic non-progression on biological plus MTX therapy (77%) than on combination triple therapy (65%). To achieve better long-term clinical and radiological outcomes in early RA patients, we should include biological therapy in our treatment protocol to align our standard of care with international guidelines, whilst also documenting radiological outcomes (eg by the Sharp van der Heijde Score[15]).

In future, radiographs of the hands and feet need to be included in all early RA patients in order to document the baseline and yearly follow-up Sharp van der Heijde Score (a composite score incorporating joint space narrowing and erosions). This affords a better understanding of radiological progression and outcomes in RA patients. Patient's quality of life should also be assessed in future trials (eg by the Short-form 36).[16]

Due to limited resources, tight control with 3- to 6-weekly follow-up was a realistic approach in our practice. An extra early RA clinic session was set up for this pilot study. Our rheumatology team shouldered the additional clinic assessment and follow-up. Though the tight control approach entails an increase in manpower and hospital costs, earlier achievement of good disease activity control should eventually ease the disease burden.

Conclusion

Our study confirmed that a tight control and protocol-driven approach could achieve better clinical outcomes in early RA patients, and resulted in

better disease activity and function. With a paradigm shift of not just achieving low disease activity in RA, the goal is to achieve remission, treat-to-target,[17] and minimise radiological damage, thus attaining better long-term outcomes. Future larger-scale, randomised controlled studies with longer follow-up are recommended. Incorporation of biological therapy in the treatment protocol, assessment of radiological outcomes, and patient's quality of life are also necessary.

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