Similar clinical outcomes in rheumatoid arthritis with more *versus* less expensive treatment strategies. Observational data from two rheumatology clinics

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Abstract

Objective

Selection of efficacious medications for rheumatoid arthritis (RA) has tremendously increased over a decade including new costly biologic agents and inexpensive conventional anti-rheumatic drugs, used in combinations for more efficacy. Treatments aim at remission or at least low disease activity. Our objective was to study whether treatment target is reached and to what cost, in patients with RA in two Nordic rheumatology clinics.

Methods

Cross sectional observational clinical data of all patients with RA seen in 2010 in two Nordic county hospital rheumatology units: Kristiansand, Norway and Jyväskylä, Finland, which both serve a population of about 275,000. Measures included patient demographic measures, clinical characteristics, disease activity, functional status, and treatments. Annual costs of medications to the society were calculated per 100 patients, using an assumption that a patient is taking current medications for one year.

Results

Patient populations from Kristiansand and Jyväskylä were similar according to age, gender, disease duration, and prevalence of RF and CCP. Disease activity was low and patients' functional status well reserved in both clinics. Almost twice as many patients in Kristiansand than in Jyväskylä (33% vs. 17%) used biologic agents. A combination of conventional anti-rheumatic drugs was currently used by <1% of patients in Kristiansand and by 37% of patients in Jyväskylä. Estimated annual costs of medications per 100 patients were €508,000 in Kristiansand and €280,000 in Jyväskylä.

Conclusions

Treatment target of remission/low disease activity and good functional status can be reached in RA using expensive and less-expensive anti-rheumatic drugs.

Key words

rheumatoid arthritis, outcomes, clinical monitoring, disease activity

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Introduction

Biologic agents are highly efficacious for treatment of rheumatoid arthritis (RA) (1). Availability of biologic agents provides a major milestone in the treatment of RA, comparable to increased use of methotrexate (MTX) over the past 20 years and joint replacements since 50 years ago. Contemporary rheumatology meetings and scientific literature is dominated by these agents.

Combinations of conventional (non-biologic) disease-modifying anti-rheumatic drugs (DMARDs) appear as effective as biologic agents for most patients with RA (2-5). Meta-analyses, extensive literature reviews, and treatment guidelines recommend a combination of conventional DMARDs in all, selected, or in patients who fail monotherapy (6-9), while a recent prominent European League against Rheumatism (EULAR) recommendation for the treatment for RA (10) ignores a combination of conventional DMARDs. In general, conventional combinations have not reached wide popularity in clinical practice.

At the advent of biologic agents, Kvien and Uhlig estimated that 15% of patients with RA need biologic agents (11). In the Finnish RA Combination trial (FIN-RACo), 20% of patients with early very active RA had a progressive disease despite conventional combination, being candidates for biologic agents (3). In the Quantitative Standard Monitoring of patients with RA study (QUEST-RA) of usual rheumatology care in 25 countries (12), biologic agent use ranged from >40% of patients to almost zero, largely associated with the wealth of the country (12), as biologic agents are expensive both from a patient's and the society's perspective (13). In fact, cost-effectiveness of biologic agents is questionable compared to conventional DMARDs (14, 15).

An identical clinical database is maintained at Sørlandet Hospital in Kristiansand, Norway and Jyväskylä Central Hospital in Jyväskylä, Finland which includes every visit of every patient. All patients with RA are treated using an identical clinical monitoring system and the same treatment target of remission or as low disease activity as possible. We aimed to study similarities and differences of patient demographic measures, clinical characteristics and outcomes, and treatments, as well as estimated costs of treatments in these two Nordic rheumatology clinics, as presented in this report.

Methods

The study was set in two rheumatology out-patient clinics in county hospitals Sørlandet Hospital in Kristiansand, Norway and Jyväskylä Central Hospital in Jyväskylä, Finland, which both serve a population of about 275,000 people.

All patients with clinical RA seen in 2010 were included.

The Treatment strategy in both clinics is to reach and maintain remission or a state of low disease activity when remission appears unattainable, generally due to long-term disease. In both clinics, there are no legal or medical insurance-based restrictions concerning the selection of medications for RA.

The clinical monitoring system is identical in these two rheumatology clinics using the same software starting in 2008. Each patient completes a self-report health questionnaire on a touch screen in the waiting area prior to the visit. Data are available for the health professional as calculated scores and as raw data. The physician records tender and swollen joint counts on an electronic homunculus, as well as an estimate of overall disease activity. Disease activity on DAS28, patient-reported outcomes, and the use of medications over time are shown on a flow sheet and time-oriented graphics. This program provides a method to collect real-time data from each patient, assists in clinical decision making and improves quality of clinical care. Data are stored in the local hospital server. Data from the most recent visit were used for analyses.

All the data described above are collected as part of clinical care to facilitate treatment decisions. The local ethics committees approved the study, which was carried out in compliance with the Helsinki Declaration.

The variables included are described in Table I. Annual costs of medications to society were calculated per 100 patients, using an assumption that a patient is taking current medications for one year.

Table I. Description of variables.

Variable	Definition
Demographic Variables	
BMI	Body mass index, self-reported weight in kilograms divided by the square of height in meters
Smoking	Current smoker, by self-report
In labor market	Full or part-time working, student, unemployed, by self-report
Disease Characteristics	
Disease duration	Calculated from clinical diagnosis to visit date
RF positive	Rheumatoid factor positive
CCP positive	Autoantibodies to citrullinated peptides
Disease activity	
SJC28	Swollen joint count including 28 joints
TJC28	Tender joint count including 28 joints
MDglobal	Doctor global assessment of disease activity on 0-100mm visual analogue scale (VAS); higher scores imply more activity
MD remission	MDglobal = 0
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
DAS28	= 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.70*Ln(ESR) + 0.014 * PTglobal, range 0-9.4; cut points for remission, low, moderate, and high disease activity 2.6, 3.2, 5.1
DAS28 remission	DAS28<2.6
Patient Reported Outcomes	
MHAQ	Modified Health Assessment Questionnaire, range 0-3; higher scores imply more disability
Pain	Pain on 0-100mm VAS
PTglobal	Patient assessment of global health on 0-100mm VAS
Fatigue	Fatigue on 0-100 VAS
RAPID3	Routine Assessment of Patient Index Data 3= mean (MHAQ * 3.33, pain, PTglobal), range 0-10
RAPID3 remission	RAPID3 <=1.0
Medications	
Medications "now"	Biologic agents or DMARDs patient is currently taking
Medications "ever"	Biologic agents or DMARDs patient has ever taken including current use
Estimated costs	Average price of biologic agents is calculated for annual use; pharmacy prices of DMARDs are used without re-imbursements

Statistics

Clinical and treatment variables were compared between the two clinics using *t*-test and Chi square test, when applicable. Crude data were compared without adjustments as patient populations were similar for age, gender, disease duration, rheumatoid factor (RF), and anti-citrullinated antibody (CCP) profile, as well as baseline values for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The percentage of patients with available data are provided (Table II). All available data are presented without imputation.

Results

Patients

The patient cohort included 1140 from Kristiansand and 1240 from Jyväskylä with similar age and gender profiles and disease duration as well as similar values for ESR and CRP at the time of the diagnosis. Smoking was more common in Kristiansand. Being part of the labour market was more prevalent in Jyvaskyla. Demographic data were available for 88%–100% of patients. (Table II).

Disease characteristics

The average disease duration was about 10 years. Similar percentage of patients were RF and/or CCP positive. Data for RF/CCP were available from 64-82% of patients. (Table II)

Disease activity was low in both clinics, mean DAS28=3.1 in Kristiansand and 2.6 in Jyväskylä. DAS28 remission was met by 54% of Jyväskylä and 35% of Kristiansand patients. All measures of disease activity were statistically significantly lower (better) in Jyväskylä *vs*. Kristiansand ($p<0.001$) except MDglobal which was similar. Disease activity data were available from 53-85% of patients (Table II).

Patient reported outcomes

The mean MHAQ was lower than 0.5 in both clinics indicating well reserved functional status. All patient outcome variables were statistically significantly better in Jyväskylä than in Kristiansand ($p<0.001$). Patient reported outcomes data were available >=92% of patients (Table II).

Medications

Twice as many patients in Kristiansand than in Jyväskylä (33% *vs*. 17%) used biologic agents. MTX was used by 49% *vs*. 72%, HCQ 3.6% *vs*. 38%, SSZ 3.6% *vs*. 27% of patients in Kristiansand and Jyväskylä, respectively. Combination of MTX+ sulfasalazine (SSZ)/hydroxychloroquine (HCQ) was currently used by <1% of patients in Kristiansand and by 37% of patients in Jyväskylä. Prednisolone was used by 63% *vs*. 52% of patients in Kristiansand and Jyväskylä, respectively. Medication data were available from 93% of patients in Kristiansand and 79% of patients in Jyväskylä (Table II). In each clinic, use of medications was similar across disease activity groups. (Table III).

Estimated costs of medications for RA were almost 2-fold in Kristiansand compared to Jyväskylä (Table IV).

Discussion

First, an identical monitoring system and clinical database as part of the infrastructure of the clinic allows direct comparison of clinical data between different clinics in different countries such as here between two county hospital rheumatology clinics in Finland and Norway. To date, comparison of clinical outcomes in the entire patient population of two separate clinics is unique.

Second, similarities in demographic data including age, sex, disease duration, and positivity for RF/CCP as well as similar values for ESR and CRP at the time of diagnosis indicate that patients represent the same population.

Table II. Clinical and treatment characteristics in patients with RA in two clinics.

	Kristiansand, NOR; data available, % patients		Jyväskylä, FIN data available, % patients		*p*-value
n.	1140	%	1240	%	
Demographic variables					
Age, mean	61	100	60	100	ns
Sex, female, %	69	100	71	100	ns
BMI, mean	25.8	88	26.5	93	0.001
Smoking, %	24	96	15	99	<0.001
In labour market, % of patients <65 years old	48	96	63	99	<0.001
Initial laboratory values at the time of diagnosis					
ESR, mean	30	46	28	81	0.042
CRP, mean	19	45	19	76	ns
Clinical data in 2010					
Disease characteristics					
Disease duration, years, mean	9.6	100	11.3	100	<0.001
RF positive, %	61	79	64	71	ns
CCP positive, %	62	74	63	64	ns
CCP or RF positive, %	69	82	71	74	ns
Disease activity					
SJC28 (0-28), mean	1.9	85	1.1	57	
TJC28 (0-28), mean	2.5	85	1.3	57	
ESR, mean	19	71	14	71	
CRP, mean	8.0	72	6.3	72	
MD global (0-100), mean	13	77	13	67	
MD remission, %	17	77	25	67	
DAS28 (0-9.4), mean	3.1	64	2.6	53	
DAS28-remission, %	35	64	54	53	
Patient Reported Outcomes					
MHAQ (0-3), mean	0.49	93	0.41	97	
Pain (0-100), mean	36	92	30	93	
PT global (0-100), mean	35	93	31	95	
Fatigue (0-100), mean	38	92	31	93	
RAPID3 (0-10), mean	2.9	94	2.5	96	
RAPID3 remission, %	22	94	29	96	
Medications		93		79	
Biologics now, %	33		17		<0.001
MTX now, %	49		72		<0.001
Prednisolone now, %	63		52		<0.001
HCQ now, %	3.6		38		<0.001
SSZ now, %	3.6		27		<0.001
Leflunomide now, %	5.8		6.3		ns
Combination of MTX+SSZ/HCQ, %	0.8		37		<0.001
Biologics ever, %	42		24		<0.001
MTX ever, %	82		90		0.062
Prednisolone ever, %	81		84		0.008
HCQ ever, %	32		69		<0.001
SSZ ever, %	26		60		<0.001
Leflunomide ever, %	22		14		<0.001
Number of DMARDs	1.9		2.7		<0.001

HCQ: hydroxychloroquine; SSZ: sulfasalazine.

Differences in disease activity and patient reported outcome variables were statistically significantly different between the clinics due to a large number of patients. We do not emphasise the differences but rather propose that these differences were not necessarily clinically meaningful and that patients represent well-treated patients with low disease activity in both clinics.

Third, our results confirm and highlight the value of routine clinical monitoring with a treatment goal, in relation to outcomes (16-18). Quantitative monitoring of RA as part of daily clinical practice has been advocated since Dr Wright's observation in 1983 that "clinicians may all too easily spend years writing 'doing well' in the notes of a patient who has become progressively crippled before their eyes …" (19). One of the earliest proposals for an active monitoring and treatment strategy for RA was expressed by Luukkainen *et al*. in 1978 "... In our opinion, gold treatment ought to be started in the early stages of RA, before the development of erosions. We are treating not only the actual inflammation of the joints but also the quality of the patient's life for many decades in the future" (20). These early visions have been enforced by current opinion leaders.

Fourth, our analyses indicate that low disease activity was seen in two clinics which use different medications for RA. Biologic agents were used 2-fold more often in Kristiansand *vs*. Jyväskylä. Every third patient in Jyväskylä used a conventional combination *vs*. <1% in Kristiansand. The use of biologic agents is highest in countries with a high gross domestic product such as Norway (21). In Finland, results of the national combination treatment trials (3, 5) have guided Finnish rheumatologists to treat their RA patients with a combination of conventional DMARDs, a treatment strategy that is comparable to biologic agents in efficacy (2, 4, 5) and superior to MTX monotherapy (22). Benefits of early suppression of disease are obvious, even without biologic agents (23, 24). Our data from these two clinics which share identical clinical monitoring and treatment goals but different agents suggest that a treatment strategy may be more important than the agents used (25). Selection of agents appear to depend on affordability of medications.

Fifth, our data provide insight to the use of oral glucocorticoids in routine care. Prednisolone was used by 63% *vs*. 52% of patients in Kristiansand and Jyväskylä, respectively, indicating that oral glucocorticoids were used as disease-modifying agents rather than a bridge therapy. Debate concerning the role of oral glucocorticoids in the treatment of RA continues (26) as they are recommended as a bridge therapy (10)

Table III. Percentage of patients taking different medications in two clinics, according to disease activity on DAS28.

	Remission n=786		Low disease activity n=305		Moderate disease activity n=526		High disease activity n=69	
	K-sand 257	JKL 529	K-sand 132	JKL 173	K-sand 288	JKL 237	K-sand 50	JKL 19
Biologic agent*	37%	15%	30%	18%	36%	17%	50%	10%
MTX + SSZ/HCQ	<1%	37%	<1%	42%	1.4%	32%	0	40%
MTX*	59%	74%	50%	73%	49%	68%	47%	60%
Pred	51%	46%	65%	64%	68%	56%	82%	60%
HCQ*	1.7%	36%	5.4%	40%	5.4%	36%	0	60%
SSZ*	4.5%	25%	5.4%	34%	2.5%	26%	2%	20%

* as monotherapy or in combination with other medications.

Table IV. Estimated annual costs from medications to the society, per 100 patients.

	Annual cost in euros to society per patient	Kristiansand	Jyvaskyla
		Multiply by	Multiply by
Biologics agents	15.000	33	17
MTX 20mg/wk, pills	100	49	72
Prednisolone, 5mg/day	25	63	52
HCQ, 300mg/day	84	3.6	38
SSZ, 2000mg/day	280	3.6	27
Leflunomide, 20mg/day	880	5.8	6.3
Total		€507.889	€279.796

or no recommendations are presented (9) while clinical use is quite extensive in many countries (12).

The Treatment of Early Aggressive RA trial (TEAR) trial (4), compared immediate active strategy to a step-up strategy in four arms: immediate MTX+etanercept or immediate triple combination therapy; step-up from MTX to MTX+etanercept or to triple combination therapy. At 2 years, mean DAS28 varied between 2.8 and 3.1 with no statistically significant differences between the groups. The TEAR results indicate that low disease activity may be reached similarly with a combination of traditional DMARDs and biologic agents. This is echoed in the present study although in a different setting.

Limitations of our study

Data were missing in up to 47% of patients due to missing formal joint count (27) which is needed for DAS28. However, patient self-report data were available in 92–96% of patients and RAPID3 was missing only in 4–6% of patients. To reveal possible systematic bias due to missing DAS28 values, patient self-report data were analysed in patients with missing *vs*. available DAS28 values. In Kristiansand, patient self-report scores and RAPID3 were similar or (statistically significantly) worse in the group of missing DAS28 vs available DAS28 values, while in Jyväskylä, scores were similar (or numerically even better) in the group of missing DAS28 vs. available DAS28 values (data not shown).

A concern has been raised that Finnish patients may present a milder disease than Norwegians. Full clinical data from the time of diagnosis would be preferable. However, as a diagnosis of RA was established in many patients long before the introduction of the current monitoring system, ESR and CRP values were the only baseline data available in both clinics. These data indicated similar initial disease activity between the clinics.

Radiographic data and prevalence of joint replacement surgery were not included in the analyses which is another limitation of the study. Furthermore, we present descriptive clinical data without randomised intervention or exposure which is regarded of a lower scientific value than randomised trials although limitations of randomised trials are obvious in chronic diseases (28).

Conclusion

Similar clinical outcomes can be reached using expensive and less-expensive anti-rheumatic drugs, which may be recognised in future recommendations and guidelines of the treatment for RA. Routine clinical monitoring of all patients may be used as a tool to reach favourable outcomes in RA patients.

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