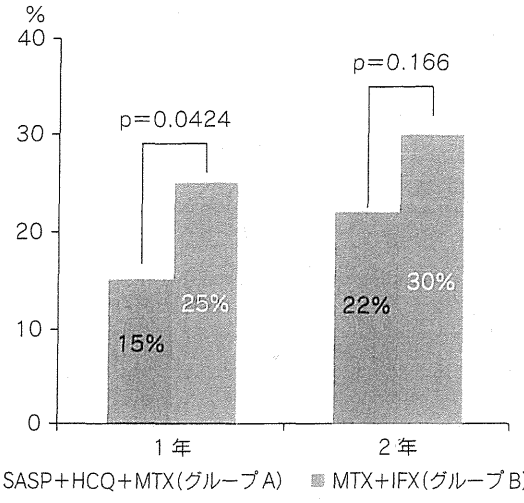
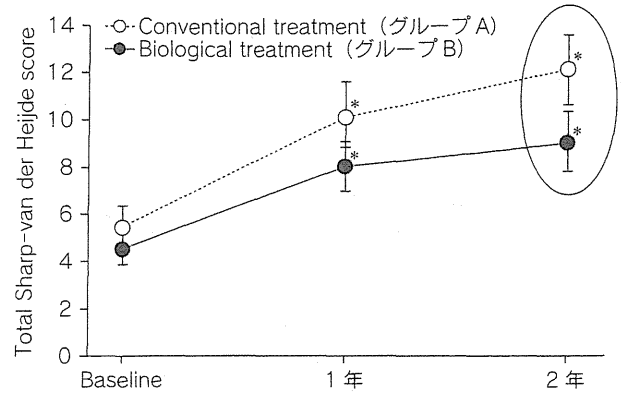
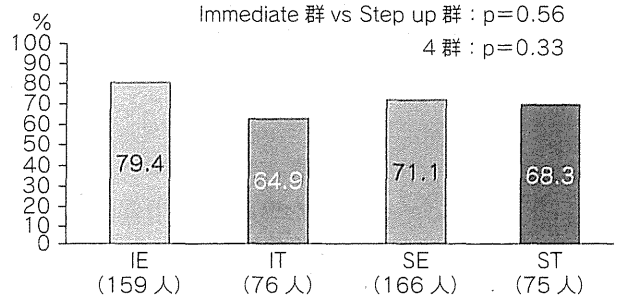


図② SWEFOT 試験 ACR50 反応率
SASP＋HCQ＋MTX：SASP 2 g/日，HCQ 400 mg/日，MTX 20 mg/日
MTX＋IFX：MTX20 mg/週＋IFX 3 mg/kg 0,2,6週，その後8週ごと
SASP：サラゾスルファピリジン，HCQ：hydroxychloroquine，MTX：メトトレキサート，IFX：インフリキシマブ
(van Vollenhoven RF *et al*, 2012[4] より引用)



図③ SWEFOT 試験 Total Sharp-van der Heijde score の推移
2年で両群間の増加した Total Sharp-van der Heijde score の差は 3.23 で，臨床的に意義のあるレベルではなかった（＊p<0.0001）.
(van Vollenhoven RF *et al*, 2012[4] より改変引用)



図④ TEAR 試験 骨破壊の進行のない（TSS< 0.5）患者の割合
IE：Immediate 群，ETN＋MTX 併用療法
IT：Immediate 群，3剤併用療法（Triple therapy，SASP＋HCQ＋MTX）
SE：Step up 群，ETN＋MTX 併用療法
ST：Step up 群，3剤併用療法
TSS：total sharp score
(Moreland LW *et al*, 2012[5] より引用)

意差が消失していた（図②）．1年時，2年時点の関節破壊はベースラインと比較して，3剤併用療法群が IFX＋MTX 群より有意に Total Sharp-Van der Heijde score は高値を示したが，両群間の差は臨床的に意義のあるレベル（5ポイント）には達していなかった（図③）．

TEAR 試験は，罹病期間3年未満 28 関節中4ヶ所の腫脹・圧痛関節のある RA 患者を対象に，MTX＋SASP＋HCQ の3剤併用療法と TNF 阻害薬であるエタネルセプト（ETN）と MTX の併用療法を比較した試験である．この試験では，最初からこれら治療を開始する immediate 群と，MTX 治療開始後6ヵ月で DAS28＞3.2 の場合に併用療法を開始する step up 群にも分けて，計4群で治療効果を比較している．その結果，4群で治療開始1年時点，2年時点での DAS28 に有意差はなく，2年時点で total sharp score は immediate 群と step up 群に差はなかった．また，ETN と MTX の併用療法群は MTX＋SASP＋HCQ の3剤併用療法群に比較し有意に骨破壊の進行を抑制していたが，やはり臨床的に意義のあるレベルには達していなかった（図④）．

これら2つの臨床試験から，MTX に反応しなかった早期 RA 患者に対する生物学的製剤の追加併用療法は有用であることに違いがないが，non biologic DMARDs の併用療法にくらべ，治療開始後短期間では疾患活動性の改善に差がでるものの，2年時点ではその差がほぼなくなり，骨破壊の進行抑制効果も有意だがその差は大きくないことが示された．すなわち，合併症やコストなどで，生物学的製剤を使用できない場合でも，この3剤併用療法は有用性が高く，医療経済的な側面を考慮して，薬剤選択を考えていく必要があることが示唆された．

3. Non biologic DMARDsの併用療法を考慮したRAの治療戦略

SWEFOT試験，TEAR試験の両試験では，MTX単独療法でも30%程度は，2年間疾患活動性が抑制されており，MTXはEULAR recommendationでも最初に使用すべき薬剤として推奨されている．前述したMTXの単独療法とnon biologic DMARDsの併用療法を比較したコクランレビューのメタ解析の結果も考慮すると，一般的にはRAの初期治療は，MTX単剤治療から開始し，すみやかなステップアップ療法をおこなうのが最良の治療戦略と考えられる．併用療法については，わが国ではHCQが使用できないためMTX＋SASP＋HCQの併用療法ができないが，MTX＋SASPにわが国で開発された他のnon biologic DMARDsを併用し，その有効性のエビデンスを積み重ね，安価で安全性の高い経済的な治療法を確立していく必要がある．

おわりに

わが国で開発された新規non biologic DMARDsとして，イグラチモドが本年9月に承認され，わが国でのnon biologic DMARDsの併用療法の組みあわせが増加する．しかしながら，本稿で紹介したように，生物学的製剤に劣らない効果がある治療として，MTX＋SASP＋HCQにはエビデンスが存在するが，他の併用療法はエビデンスに乏しいのが実情で，わが国でのみ使用できるnon biologic DMARDsを用いた併用療法の臨床試験を進める必要がある．さらに，tofacitinibのようなJAK阻害薬が使用可能となれば，RAの治療戦略が再び変化し，生物学的製剤を使用せずとも早期診断してこれら薬剤を有効に使用することにより，RA患者の予後がさらに改善するものと考えられる．

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EXTENDED REPORT

A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry

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ABSTRACT

Purpose To compare the effectiveness of anti-tumour necrosis factor (TNF) agents in biologically naive and 'switched' rheumatoid arthritis (RA) patients.

Methods RA patients enrolled in the CORRONA registry newly prescribed adalimumab (n=874), etanercept (n=640), or infliximab (n=728) were stratified based on previous anti-TNF use. Clinical effectiveness at 6, 12 and 24 months was examined using the modified American College of Rheumatology response criteria (mACR20/50/70) and achievement of remission (28-joint disease activity score (DAS28) and clinical disease activity index (CDAI)) in unadjusted and adjusted analyses. The persistence of anti-TNF treatment was examined using Cox proportional hazard models.

Results Among 2242 patients (1475 biologically naive, 767 switchers), mACR20, 50 and 70 responses were similar (p>0.05) for adalimumab, etanercept and infliximab at all time points, as were rates of CDAI and DAS28 remission (p>0.05). Response and remission outcomes were consistently inferior for switched versus biologically naive patients. The adjusted OR for achieving an mACR20 response was 0.54 (95% CI 0.38 to 0.76) in first-time switchers and 0.42 (95% CI 0.23 to 0.78) in second-time switchers versus biologically naive patients at 6 months. The adjusted OR for achieving DAS28 remission were 0.29 (95% CI 0.15 to 0.58) for first-time switchers and 0.26 (95% CI 0.08 to 0.84) for second-time switchers. Persistence was higher in biologically naive patients, for whom persistence was highest with infliximab.

Conclusions No differences in rates of drug response or remission were observed among the three anti-TNF. Infliximab was associated with greater persistence in biologically naive patients. Response, remission and persistence outcomes were diminished for patients who switched anti-TNF.

Over the past decade, anti-tumour necrosis factor (TNF) therapies have become the most frequently prescribed class of biological agents for the treatment of rheumatoid arthritis (RA) in the USA and Europe. Currently, there are five anti-TNF agents approved by the European Medicines Agency and the US Food and Drug Administration, with varying structures, dosing and pharmacokinetics. Despite these differences, they all block TNF, and two randomised clinical trial (RCT) meta-analyses of three commonly prescribed anti-TNF (adalimumab, etanercept and infliximab) concluded that the three anti-TNF demonstrated comparable efficacy.[1 2] However, these meta-analyses have been criticised, and their findings conflict with the results reported in two European registry studies demonstrating that adalimumab and etanercept users have better clinical responses than infliximab users.[3 4] Those reports originated from European countries with more restricted access to biological agents and dosage restrictions.

An important caveat to the application of anti-TNF RCT results to RA patients in the clinic is that the vast majority of the RCTs were conducted in biologically naive patients, particularly in those without a previous history of anti-TNF treatment. However, intraclass switching of anti-TNF agents is common in clinical practices in Europe and the USA.[5–8] Currently, there is inadequate evidence regarding the benefits of this strategy. As a result, switching patients to a different anti-TNF agent is restricted in certain European countries. Comparative effectiveness research using observational data sources has gained broader support in Europe and the USA across clinical disease areas.[9–11]

Comparative effectiveness studies using observational data from registries represent a promising alternative to RCT for comparing interventions and therapies between biologically naive patients and patients who switch anti-TNF.[11] This is important because rheumatologists in the USA and many European countries prescribe anti-TNF agents to RA patients with markedly lower disease activity than RCT populations.[12–14] Given that comparative effectiveness data for US-based cohorts are lacking, the aim of the present study was to compare the clinical effectiveness of specific anti-TNF agents and the strategy of intraclass switching in a large US cohort of RA patients using the Consortium of Rheumatology Researchers of North America (CORRONA) registry. In particular, we sought to compare composite rates of drug response and remission outcomes as well as the persistence of anti-TNF treatment over a 2-year period.

Table 1 Baseline characteristics of the study cohort stratified by previous exposure to anti-TNF and newly prescribed anti-TNF agent

	Biologic naive				First-time switchers*			
Characteristics	**ADA N=460**	**ETA N=480**	**INF N=535**	**p Value†**	**ADA N=311**	**ETA N=139**	**INF N=166**	**p Value†**
Demographics								
Women	78%	76%	72%	0.06	82%	79%	82%	0.72
Age (years)	55±12	54±13	61±13	<0.001	56±13	56±13	56±12	0.83
Healthcare coverage‡								
Private insurance	78%	81%	72%	0.04	79%	81%	74%	0.39
Medicare	27%	24%	45%	<0.001	34%	35%	34%	0.98
Medicaid	7%	9%	6%	0.30	9%	6%	5%	0.23
Clinical								
Duration of RA (years)	8.9±9.5	8.8±9.2	9.6±9.9	<0.001	12.7±9.7	10.6±10.0	11.8±9.4	0.09
Tender joint count	7.1±7.1	6.4±6.2	6.3±6.7	0.11	7.6±7.1	6.6±6.8	6.3±6.9	0.14
Swollen joint count	7.6±6.5	6.5±5.8	8.2±6.9	<0.001	6.7±6.3	6.9±6.5	7.4±7.00	0.57
Patient global assessment (0–100 mm)	41.2±27.5	40.1±24.7	38.7±24.9	0.34	44.4±25.3	42.9±27.3	38.7±25.5	0.09
Patient pain assessment (0–100 mm)	43.3±28.0	41.5±24.7	41.5±25.8	0.48	45.7±25.5	46.0±26.0	41.9±24.9	0.26
Physician global assessment (0–100 mm)	36.9±20.5	33.5±20.3	34.4±20.9	0.03	37.3±22.3	33.3±20.5	32.8±22.2	0.05
mHAQ score	0.5±0.5	0.5±0.5	0.4±0.5	0.11	0.6±0.5	0.6±0.5	0.4±0.4	0.01
ESR (mm/h)	25.7±23.3	24.2±19.8	28.2±23.2	0.19	28.9±23.2	28.1±23.5	28.2±22.0	0.96
DAS28	4.49±1.6	4.48±1.4	4.53±1.4	0.91	4.55±1.5	4.39±1.3	4.46 ±.6	0.79
CDAI	22.3±13.7	20.2±12.3	22.0±13.4	0.04	22.4±14.3	21.1±13.4	20.6±13.9	0.43
Disease activity per CDAI				0.15				0.69
High (>21)	21	22	22		23	21	25	
Moderate (>5–≤21)	37	41	34		33	39	36	
Low (>2.2–≤5)	42	37	44		44	40	39	
BMI	29.2±7.1	29.5±7.6	29.6±7.5	0.67	28.6±7.3	30.5±7.7	29.2±6.6	0.04
Disabled	11	11	10	0.79	24	12	17	0.01
Medication at entry								
Prednisone	35	33	33	0.80	35	35	33	0.81
Methotrexate	68	61	68	0.05	53	63	60	0.13
Methotrexate dose								
≤7.5 mg	22%	17%	28%		24%	15%	23%	
10–17.5 mg	43%	49%	38%		37%	48%	36%	
≥20 mg	35%	34%	35%		40%	36%	41%	
No of previous DMARD	0.7±1.0	0.7±1.0	0.7±1.0	0.73	2.1±1.4	1.5±1.3	1.8±1.3	<0.001

Data shown are percentages of patients or mean±SD.
*Second-time switchers, including 103 switched to adalimumab, 21 to etanercept and 27 to infliximab, are not included due to relatively small sample size.
†p Values are derived from analysis of variance for continuous measures and Fisher's exact test for dichotomous variables.
‡Categories are not mutually exclusive.
ADA, adalimumab; BMI, body mass index; CDAI, clinical disease activity index; DAS28, disease activity score employing 28-joint count; DMARD, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; ETA, etanercept; INF, infliximab; mHAQ, modified health assessment questionnaire; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

METHODS

Data source

The CORRONA registry is an independent prospective observational cohort of patients with arthritis who are enrolled by participating rheumatologists in both academic and private practice sites. As detailed previously,[15 16] CORRONA is governed by a board of academically affiliated US rheumatologists. CORRONA has no governance or ownership ties to the pharmaceutical industry. CORRONA receives funding from multiple pharmaceutical manufacturers to support the registry.

CORRONA data collection began in 2002; data collected to 11 March 2008 are included in the current analyses. Up to 2008, there were 83 sites across 33 states in the USA, and approximately 200 rheumatologists have enrolled a total of 19 902 patients, including 16 696 with RA. Approximately 22% of the sites were academic sites and 78% were private sites. The geographical distribution of patients in the registry across the USA was the northeast region 34%, midwest region 24%, south region 28% and west region 14%. Patients were enrolled into the CORRONA registry at the time of a routine clinic visit. Enrolment into the CORRONA registry remains active. Both patient and physician questionnaires are filled out during routine clinical encounters. Completed questionnaires are faxed or mailed to a central processing site. Approvals for data collection and analyses were obtained for academic and private practice sites from local and central institutional review boards, respectively.

Study population

Among the 16 696 patients with RA enrolled in the CORRONA registry, 2530 were newly prescribed an anti-TNF agent with at least one follow-up visit between 4 February 2002 and 11 March 2008. No disease activity or comorbidity exclusion criteria were required for RA patients enrolled into the consortium registry. For the purposes of this study, the 162 RA patients in remission at baseline, defined by a clinical disease activity index (CDAI)[17] score of 2.8 or less or a disease activity score based on 28 joints (DAS28) and erythrocyte sedimentation rate (ESR) less than 2.6 were excluded from the study population. Patients with a previous history of the use of a non-TNF agent (N=126) were also excluded, resulting in 2242 RA patients included in this analysis. Among these 2242 patients, 1475 were biologically naive, 616 were first switchers and 151 were switching to their second or more biological agent. A flowchart describing the study population in greater

Table 2 Crude response and remission rates at 6 and 12 months among adalimumab, etanercept and infliximab users in those who were biologically naive

	6 Months			12 Months		
	INF	ADA	ETA	INF	ADA	ETA
mACR response						
No of patients	230	235	222	182	190	178
mACR 20						
Responders (%)	26.5	30.6	37.4	26.9	26.8	31.5
Adjusted OR*	1.00	0.95 (0.60–1.50)	1.37 (0.94–1.99)	1.00	0.96 (0.56, 1.64)	1.35 (0.84, 2.18)
mACR50						
Responders (%)	14.3	19.6	26.6	20.3	17.4	20.8
Adjusted OR*	1.00	1.03 (0.52, 2.01)	1.75 (0.99, 3.09)	1.00	0.72 (0.46–1.13)	1.03 (0.62–1.70)
mACR70						
Responders (%)	9.6	10.2	9.9	12.1	12.1	11.8
Adjusted OR*	1.00	0.76 (0.41–1.42)	0.81 (0.42–1.56)	1.00	0.83 (0.46–1.49)	1.04 (0.61–1.78)
CDAI remission						
No of patients	254	249	242	199	202	189
Responders (%)	15.7	13.7	16.1	17.1	12.9	18.5
Adjusted OR†	1.00	0.83 (0.42–1.63)	1.18 (0.65–2.14)	1.00	0.69 (0.42–1.15)	1.15 (0.61–2.12)
DAS28 remission						
No of patients	103	107	116	71	75	72
Responders (%)	28.2	25.2	28.4	33.8	33.3	37.5
Adjusted OR†	1.00	0.72 (0.48–1.08)	0.95 (0.43–2.08)	1.00	0.89 (0.39–2.00)	1.01 (0.47–2.12)

*Adjusted for duration of RA, joint counts, patient global, age, mHAQ, disability, use of methotrexate and year of initiation.
†Adjusted for duration of RA, baseline disease activity, age, mHAQ, disability, use of methotrexate and year of initiation.
ADA, adalimumab; CDAI, clinical disease activity index; DAS28, disease activity score employing 28-joint count; ETA, etanercept; INF, infliximab; mACR, modified American College of Rheumatology.

detail can be found in supplementary figure S1 (available online only).

Measures and data collection

Data were collected during the study period from physician assessment and patient questionnaires completed during clinical encounters. Patients were followed as frequently as every 3 months. For this dataset, the mean time between visits was 4.7 months and the median time between visits was 3.8 months. Non-biological and biological disease-modifying antirheumatic drugs (DMARD), including anti-TNF agents, were recorded at the time of the clinical encounter. Data elements also documented at the time of a clinical encounter that are relevant to the current analysis included 28 tender and swollen joint counts, physician and patient global assessments of disease activity, patient assessment of pain, the modified health assessment questionnaire (HAQ) assessing physical function and ESR. Across the 2242 patients, data on tender and swollen joint counts were complete in 2210 (98.6%) patients. All components of the CDAI were completed for 2069 (92.3%) patients. Acute phase reactant data were recorded from laboratory tests obtained within 10 days of the clinical encounter, but collection of laboratory data was not mandated by the registry protocol. ESR values were available for 1210 (54%) patients. Insurance data was available for 73.5% of patients. Completeness was high for data required for the CDAI (>92%).

Drug exposure cohorts

Patients initiating adalimumab, etanercept and infliximab were stratified into one of three cohorts. Biologically naive patients initiating an anti-TNF agent were defined as patients with no lifetime history of treatment with anakinra, other anti-TNF agents, abatacept or rituximab. First-time switchers were defined as patients initiating an anti-TNF agent with a history of previous treatment with a different anti-TNF agent. Second-time switchers were defined as patients with a history of previous treatment with two different anti-TNF agents. Within each of the three cohorts, comparisons among the three individual anti-TNF agents (adalimumab, etanercept and infliximab) were performed.

Registry outcomes

Responsiveness to anti-TNF therapy was assessed using the modified American College of Rheumatology (ACR) 20, 50 and 70 response criteria without the requirement for an acute phase reactant to maximise the amount of patient data available for analysis. These measures have been previously defined and validated.[18 19] A modified ACR20 response required a 20% or greater improvement in tender and swollen joint counts, as well as in two or more of the following four ACR response components: physician global assessment, patient global assessment, patient global pain and modified HAQ. The modified ACR50 and 70 responses were calculated using the same criteria, but requiring at least 50% and 70% improvement, respectively. Disease remission outcomes were defined as a DAS28–ESR score less than 2.6[20] and a CDAI score, which does not require an acute phase reactant, of 2.8 or less.[17] Continuation or persistence of treatment with the newly prescribed anti-TNF agent was defined as the duration of time from anti-TNF initiation to discontinuation.

Statistical analysis

Patient clinical and demographic characteristics were compared within the three strata of previous anti-TNF exposure by specific agent. For continuous measures, means and SD were estimated and analysis of variance was used to assess the statistical significance of any differences among the groups. For dichotomous measures, percentages were estimated and Fisher's exact test was used to assess the significance of differences among groups.

For modified ACR20, 50 and 70 response, patients who discontinued the newly prescribed anti-TNF agent were categorised as

Table 3 Secondary analysis of response and remission rates in biologically naive patients: dose escalation imputed as non-response

	6 Months			12 Months		
	INF	ADA	ETA	INF	ADA	ETA
mACR response						
No of patients	230	235	222	182	190	178
mACR 20						
Responders (%)	25.7	28.9	37.4	23.6	25.2	31.5
Adjusted OR	1.00	0.97 (0.63–1.49)	1.50 (1.06–2.13)	1.00	1.03 (0.2–1.70)	1.60 (0.98–1.69)
mACR50						
Responders (%)	13.5	18.7	26.6	18.1	16.8	20.8
Adjusted OR	1.00	1.16 (0.64–2.12)	2.04 (1.24–3.35)	1.00	0.73 (0.47–1.15)	1.10 (0.65–1.86)
mACR70						
Responders (%)	9.1	9.8	9.9	11.0	11.6	11.8
Adjusted OR	1.00	1.04 (0.62–1.75)	1.10 (0.58–2.09)	1.00	1.03 (0.59–1.81)	1.07 (0.62–1.85)
CDAI remission						
No of patients	254	249	242	199	202	189
Responders (%)	15.4	12.9	16.1	16.1	12.4	18.5
Adjusted OR	1.00	0.78 (0.37–1.62)	1.19 (0.64–2.22)	1.00	0.69 (0.43–1.10)	1.20 (0.63–2.27)
DAS28 remission						
No of patients	103	107	116	71	75	72
Responders (%)	26.2	25.2	28.4	28.1	32.0	37.5
Adjusted OR	1.00	1.08 (0.74–1.58)	1.26 (0.68–2.33)	1.00	1.22 (0.64–2.35)	1.57 (0.91–2.72)

ADA, adalimumab; CDAI, clinical disease activity index; DAS28, disease activity score employing 28-joint count; ETA, etanercept; INF, infliximab; mACR, modified American College of Rheumatology.

non-responders (ie, no modified ACR20 50 or 70 response or no DAS28–ESR or CDAI remission) for any study visit after discontinuation, using intention-to-treat analyses with non-responder imputation approach as previously applied.[13 21] Unadjusted ACR response rates were determined at 6, 12 and 24 months following the start of the newly prescribed anti-TNF using 3-month time windows for capturing study visits. Unadjusted and adjusted OR comparing response rates among anti-TNF agents were estimated using multivariable logistic regression models and were reported with estimated 95% CI. Covariates associated with either anti-TNF agent selection or response to treatment were considered as possible confounders and included patient demographics, disease activity and severity measures, previous medication usage, history of comorbidities and years since anti-TNF agent initiation Sensitivity analyses were carried out applying a completer's analysis approach. Similar methodology was employed to assess remission based on the DAS28–ESR and CDAI cut points defined above.

Treatment persistence was estimated using survival analysis methods. Time from initiation to discontinuation of the anti-TNF or to last follow-up visit was estimated based on the initiation visit dates and discontinuation (or last follow-up) dates. Unadjusted Kaplan–Meier survival curves were estimated for each of the three study cohorts, as well as individually for anti-TNF agents within each cohort. Log rank tests were used to test the null hypothesis of no differences among the Kaplan–Meier survival curve estimates. Proportional hazard assumptions were assessed graphically by comparing survival curves estimated by Cox regression models and Kaplan–Meier estimates and by assessing the log–log survival plots. Cox proportional hazard regression models estimated unadjusted and adjusted HR of discontinuation.

For each of the study outcomes, comparisons were performed among the three cohorts (biologically naive, first-time switchers and second-time switchers), and among the three anti-TNF agents stratified within the biologically naive and first-time switcher cohorts. For the primary analysis of persistence, we used the visit dates of reported initiation and visit dates of reported discontinuation. An analysis was also carried out in which we used dates as described above for those who indicated starting or discontinuing 'at the visit' but for those indicating 'since last visit' we substituted the date halfway between visits with little change in results. Comparisons of the three anti-TNF agents among second-time switchers were not performed due to small sample sizes within this cohort. We also performed sensitivities that incorporated major changes in dose/frequency in the survival analyses and imputed non-response for major dose/frequency escalations. We distinguished high versus low dose/frequency for adalimumab as 40 mg weekly versus every 2 weeks, and for infliximab using the cutpoint of of greater than 6 mg/kg every 8 weeks or equivalent based on a previously published cutpoint.[22]

To allow comparison with other registries and RCT, crude response and remission rates were stratified on the basis of whether or not patients met the eligibility criteria from three major published controlled trials.[12] As the registry records 28-joint counts, we estimated 28-joint count equivalents for the RCT 66-joint count requirements based on the 28-joint validation methodology previously described.[12] For the 66-joint count threshold of six or more tender and swollen joints, we applied the estimated 28-joint count equivalent of four of more joints such that patients who were deemed RCT eligible had four or more swollen joints, four or more tender joints and 45 min or more of morning stiffness at the time of registry enrollment. Power calculations varied across study outcomes for 6-month modified ACR outcomes. In biologically naive patients, we had 93% power to detect an OR of 2.0. For DAS28 remission at 6 months we had 76% power to detect an OR of 2.25.

RESULTS

Demographic and clinical characteristics

The study population consisted of 2242 RA patients; 1475 patients were biologically naive before initiating anti-TNF therapy, 616 had switched to a second anti-TNF agent (termed 'first-time switchers') and 151 had switched to their third anti-TNF agent (termed 'second-time switchers'). The baseline

Table 4 Unadjusted response and remission rates and adjusted likelihoods of achieving response/remission over time stratified by anti-TNF switch status

	6 Months			12 Months		
	Biologically naive	First-time switcher	Second-time switcher	Biologically naive	First-time switcher	Second-time switcher
mACR response						
No of patients	687	319	73	550	251	67
mACR 20						
Responders	30.5%	19.9%	17.3%	28.5%	14.7%	18.7%
Adjusted OR (95% CI)†	1	0.54 (0.38 to 0.76)*	0.42 (0.23 to 0.78)*	1	0.44 (0.30 to 0.66)*	0.50 (0.25 to 0.99)*
mACR50						
Responders	20.2%	9.4%	9.9%	18.9%	8.8%	9.3%
Adjusted OR (95% CI)†	1	0.42 (0.27 to 0.65)*	0.42 (0.20 to 0.86)*	1	0.49 (0.30 to 0.78)*	0.41 (0.17 to 0.99)*
mACR70						
Responders	10.3%	2.6%	4.9%	11.4%	3.7%	4.0%
Adjusted OR (95% CI)†	1	0.28 (0.14 to 0.55)*	0.50 (0.19 to 1.32)	1	0.39 (0.19 to 0.80)*	0.23 (0.05 to 1.05)
CDAI remission						
No of patients	745	334	75	590	263	67
Responders	15.4%	7.3%	1.2%	16.2%	8.8%	5.3%
Adjusted OR (95% CI)‡	1	0.57 (0.36 to 0.90)*	0.09 (0.01 to 0.71)*	1	0.63 (0.38 to 1.04)	0.32 (0.10 to 1.03)
DAS28–ESR remission						
No of patients	326	136	41	218	85	27
Responders	25.1%	7.6%	7.5%	29.3%	10.3%	9.4%
Unadjusted OR (95% CI)‡§	1	0.21 (0.08 to 0.56)*	0.29 (0.07 to 1.22)*	1	0.21 (0.07 to 0.65)*	0.31 (0.06 to 1.59)

Data presented are the percentage of patients or adjusted OR (95% CI).
*$p<0.05$.
†Derived via multivariate logistical regression analyses adjusted for age, disease duration, swollen joint count, tender joint count, modified HAQ disability index, patient global assessment, self-reported disability, methotrexate use and year since anti-TNF initiation.
‡Derived via multivariate logistical regression analyses adjusted for age, disease duration, baseline disease activity, self-reported disability, methotrexate use and years since anti-TNF initiation.
§Inadequate sample size for examination of adjusted likelihoods.
CDAI, clinical disease activity index; DAS28, disease activity score employing 28-joint count; ESR, erythrocyte sedimentation rate; mACR, modified American College of Rheumatology; TNF, tumour necrosis factor.

characteristics based on anti-TNF agent among the biologically naive and first-time switchers are displayed in table 1. Infliximab users were more likely to be older and have Medicare insurance compared with the other biologically naive patients. Among first-time switchers, adalimumab users were more likely to be disabled and were exposed to a greater number of previous DMARD. Among the second time switchers (adalimumab n=103, etanercept n=21 and infliximab n=27), users of etanercept were more likely to be women (data not shown). When examining patients based on overall switching status and not by specific agent, disease duration and the number of previous DMARD, both increased as the number of anti-TNF switches increased. Similarly, higher (worse) modified HAQ, patient global and patient pain scores, and larger proportions of patients reporting disability were observed with more anti-TNF switches. Of note, the overall mean DAS28–ESR (4.5) and CDAI (21.5) scores were within the defined ranges of moderate disease activity levels (data not shown).

Anti-TNF treatment

The median dose of infliximab, exclusive of the loading protocol, was 5.5 mg/kg every 8 weeks in biologically naive patients, 5.6 mg/kg every 8 weeks in first-time switchers and 7.1 mg/kg every 8 weeks in second-time switchers. The majority of patients prescribed adalimumab received 40 mg every other week (86.5% of biologically naive patients, 75.4% of first-time switchers and 53.7% of second-time switchers). Among patients prescribed etanercept, dose escalation information was not collected because the two approved dosing options (ie, 25 mg twice weekly and 50 mg once weekly) are considered equivalent.

Response and remission rates by newly prescribed anti-TNF agent

Achievement of modified ACR20 occurred in 26.8–35.4% of biologically naive anti-TNF users at 6 months (table 2). At 12 months the rates were 26.7–32.4%. Response rates using the modified ACR50 and modified ACR70 were 15.0–26.5% and 10.0–12.3%, respectively. In adjusted analyses, the likelihood of achieving modified ACR20, 50 or 70 response outcomes was not significantly different among the three anti-TNF agents in biologically naive patients (table 2). Also in biologically naive patients, remission rates based on the CDAI were 15.1–16.6% at 6 months and 12.8–20.7% at 12 months. DAS28 remission rates were slightly higher (23.2–27.1% at 6 months and 27.8–32.1% at 12 months). Within the biologically naive patients, no differences in the likelihood of achieving remission among specific anti-TNF agents were observed using the CDAI and DAS28 remission definitions (table 2). Similar patterns of response and remission were observed in first-time switchers (see supplementary table S1, available online only). Response and remission results at 24 months were consistent in both biologically naive patients and first-time switchers (data not shown). For the modified ACR20/50/70 outcomes, as well as the DAS28/CDAI remission outcomes, consideration of dose/frequency escalation as 'non-responders' as a secondary analysis failed to demonstrate any consistent patterns in biologically naive patients across the three anti-TNF agents (table 3).

Unadjusted response and remission rates by switching status

In the full study cohort without any stratification by disease activity, achievement of a modified ACR20 response occurred in 30.5%, 28.5% and 23.4% of biologically naive patients at 6, 12 and 24 months, respectively (table 4). Respective modified ACR20 response rates were 19.9%, 14.7% and 13.9% in first-time switchers and 17.3%, 18.7% and 15.7% in second-time switchers. The modified ACR 50 and modified ACR70 response rates were similarly higher in biologically naive patients than in both first and second-time anti-TNF switchers.

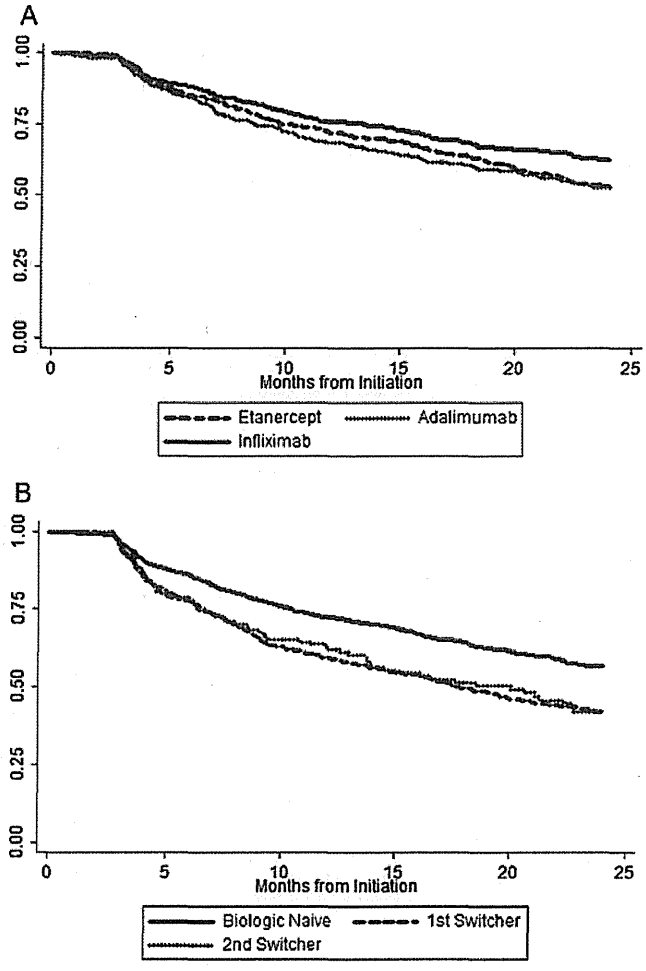

Figure 1 Drug persistency for (A) specific anti-TNF agents in biologically naïve patients and (B) biologically naïve patients versus those switched to anti-TNF agents. TNF, tumour necrosis factor.

Lower remission rates were also observed among anti-TNF switchers versus biologically naive patients for both DAS28–ESR and CDAI remission (table 4).

Adjusted response and remission comparisons based on switching status

After adjustment for differences in baseline characteristics, the likelihood of achieving a modified ACR20, 50 or 70 response was consistently reduced in first-time switchers versus biologically naive patients at 6, 12 and 24 months (table 4). For example, using biologically naive patients as the reference group, the adjusted OR for first-time switchers in achieving a modified ACR20 response was 0.54 (95% CI 0.38 to 0.76) at 6 months, 0.44 (95% CI 0.30 to 0.66) at 12 months and 0.54 (95% CI 0.31 to 0.93) at 24 months. For second-time switchers, a reduced likelihood of response was also observed, although CI crossed unity at some time points.

A similar pattern of response was observed for clinical remission (table 4). At 6 months, the adjusted OR for achieving DAS28–ESR remission was 0.21 (95% CI 0.08 to 0.56) for first-time switchers and 0.29 (95% CI 0.07 to 1.22) for second-time switchers versus biologically naive patients.

Similarly, using the CDAI remission definition, first-time switchers (OR 0.57, 95% CI 0.36 to 0.90) and second-time switchers (OR 0.09, 95% CI 0.01 to 0.71) were significantly less likely to achieve remission when compared with biologically naive patients at 6 months (table 4). Reduced likelihoods of achieving DAS28–ESR and CDAI remissions were also observed at 12 and 24 months, although with wider CI. Sensitivity analyses applying a completer's analysis approach instead of non-responder imputation yielded comparable results (data not shown).

Persistence of treatment with newly prescribed anti-TNF

Based on Kaplan–Meier curve estimates (figure 1A,B), the proportions of biologically naive patients with persistence of the new anti-TNF treatment to 12 and 24 months were 76% and 63%, respectively, with infliximab versus 72% and 53% with etanercept, and 68% and 53% with adalimumab (table 5). In adjusted analyses, discontinuation was more likely in biologically naive patients receiving adalimumab (OR 1.42, 95% CI 1.12 to 1.80) or etanercept (OR 1.27, 95% CI 1.00 to 1.61) versus infliximab. Additional modelling to address dosing titration suggestive of incomplete response was performed, and examined time to drug discontinuation or dose/frequency escalation. These models demonstrated a different pattern. Relative to infliximab (HR 1.0) among biologially naive patients, the HR for discontinuation/dose escalation for etanercept was 0.77 (95% CI 0.63 to 0.96) and for adalimumab 1.11 (95% CI 0.90 to 1.37), reflecting the impact of dose/frequency escalation. No differences among the three agents were observed among first-time switchers (table 5). As demonstrated in figure 1B, patients who switched drugs remained on their anti-TNF agent for shorter time periods than biologically naive patients.

Patients meeting commonly applied RCT eligibility criteria

Response and remission rates differed based on disease activity (see supplementary table S2, available online only). Among patients who met three commonly applied RCT eligibility criteria for enrollment in RCT, modified ACR20 response rates were higher at all time points (43.8%, 38.2% and 30.6% at 6, 12 and 24 months) compared with respective rates in patients who had less severe disease and were thus not RCT eligible (19.1%, 17.1% and 15.2%). Consistent stratification patterns were observed for modified ACR50 and modified ACR70 response rates (see supplementary table S2, available online only). Conversely, RCT-ineligible patients (ie, those with lower disease activity) were more likely to achieve CDAI remission (14.0%, 14.0% and 12.8% at months 6, 12 and 24) than the RCT-eligible patients with more active disease (10.9%, 10.4% and 11.4% at months 6, 12 and 24). Similar findings were observed using the DAS28–ESR remission criteria (data not shown).

DISCUSSION

In this large US registry study, the majority of RA patients prescribed anti-TNF agents had low or moderate disease activity, demonstrating markedly lower disease activity than previously reported in the pivotal anti-TNF RCT and European registries.[3 4 23] For both biologically naive and switched patients, we observed no differences in drug response or remission outcomes among adalimumab, etanercept and infliximab users. However, the likelihood of achieving both response and remission outcomes were consistently greater for biologically naive patients than anti-TNF switchers. Persistence was noted to be higher for biologically naive patients, with the highest persistence noted for infliximab users. These comparative effectiveness results derived from a multi-centred US registry differ from the results reported in two large European registries.[3 4]

The dosing patterns in our US-based registry were different than dosing patterns reported in the European registries. In particular, the dose of infliximab was approximately 3.5 mg/kg in

Table 5 The unadjusted persistence rates and adjusted likelihood of drug discontinuation based on anti-TNFα switching status*

	Persistence rate			
	12 months (95% CI)	24 months (95% CI)	Adjusted HR (95% CI)	p Value
TNF inhibitor switching status				
Biologically naive (referent)	72% (70% to 75%)	57% (54% to 60%)	1	
First switchers	60% (55% to 64%)	42% (37% to 47%)	1.42 (1.22 to 1.67)	<0.001
Second switchers	63% (54% to 70%)	42% (33% to 51%)	1.35 (1.03 to 1.76)	0.028
Interdrug comparisons				
Biologically naive				
Infliximab (referent)	76% (72% to 80%)	63% (58% to 67%)	1	
Adalimumab	68% (64% to 73%)	53% (47% to 58%)	1.42 (1.12 to 1.80)	0.004
Etanercept	72% (68% to 76%)	53% (48% to 59%)	1.27 (1.00 to 1.61)	0.047
First switchers				
Infliximab (referent)	65% (56% to 72%)	43% (34% to 52%)	1	
Adalimumab	57% (51% to 62%)	42% (35% to 48%)	1.14 (0.84 to 1.55)	NS
Etanercept	60% (50% to 68%)	41% (31% to 50%)	1.01(0.71 to 1.44)	NS

*Results are presented as HR with 95% CI in parentheses; the models adjusted for age, gender, patient and provider assessments of disease activity, self-reported disability, comorbidity, methotrexate use and year of anti-TNF initiation.
NS, not significant; TNF, tumour necrosis factor.

the Danish registry and 3 mg/kg in the Dutch registry, whereas the mean dose was approximately 5.5 mg/kg in our study.[3 4] Similarly, dose escalation from adalimumab 40 mg every 2 weeks to weekly was more common in our US registry than European registries. These dosing differences further emphasise the potential limitations of applying the results of European-based registry results to RA patients in the USA[21] and vice versa. In particular, this difference in dose escalation of infliximab, and possibly also adalimumab, may explain the conflicting comparative effectiveness results from our US registry and the two European registry studies.[3 4]

In fact, our study results are consistent with the two published RCT meta-analyses, concluding that there was no difference in the efficacy among the three anti-TNF drugs. However, these meta-analyses have been criticised for lacking statistical power and for including study arms of infliximab with drug dosages not frequently prescribed, especially in European countries.[1–4] The Dutch Rheumatoid Arthritis Monitoring (DREAM) register reported significantly greater reductions in DAS28 and HAQ-DI for both adalimumab and etanercept versus infliximab.[4] These findings were further supported by the nationwide Danish Biologics (DANBIO) registry, in which patients receiving either adalimumab or etanercept were more likely to achieve a ACR50, ACR70 and European League Against Rheumatism (EULAR) moderate/good response than patients prescribed infliximab.[3] In both studies, drug persistence was also lowest for infliximab. However, as previously noted, the median dosage and frequency of administration of infliximab in these two studies were markedly different from our experience in the US-based CORRONA registry. Alternatively, we may have failed to detect a difference due to a type II error. Therefore, these important differences may partly explain differences in study results derived from US registries, European registries and RCT.

The effectiveness of anti-TNF switching for incomplete responders to a first anti-TNF agent has also been examined primarily in European studies. Investigators using the South Swedish Arthritis Treatment Group (SSATG) register examined drug responsiveness and remission outcomes in patients receiving their second or third anti-TNF agent, and found diminished ACR response and DAS28 remission rates in patients who switched versus first-time users.[8] The largest published study of treatment response among anti-TNF switchers was the European-based open-label clinical trial of adalimumab, the Research in Active Rheumatoid Arthritis (ReAct) trial.[24] Among patients who had a history of treatment with etanercept and/or infliximab, use of adalimumab resulted in robust ACR response and remission rates, but these proportions were lower among adalimumab-treated patients who switched. A recent systematic review, based primarily on a small number of European registry studies, concluded that responses to a subsequent anti-TNF agent were diminished when the switch was due to lack of efficacy.[25] To our knowledge, no comparative effectiveness studies from US registries have been published for anti-TNF switching in RA patients.

Drug persistence studies of anti-TNF agents in RA patients have also been published, and may be the outcome measure most strongly influenced by a nation's healthcare system and drug access policies. Persistence has been reported as a surrogate measure of drug effectiveness, but is also influenced by tolerability, toxicity, cost and relative availability. When comparing persistence across individual agents, investigators using the German biological agent registry as well as the British Society for Rheumatology Biologics Register in the UK did not find differences in persistence among the three anti-TNF agents.[6 26] In contrast, the DANBIO and DREAM registries, as well as a Swedish registry, observed that the risk of discontinuation was higher for infliximab users than adalimumab or etanercept users.[27] In contrast, the results from a recent study from a US administrative claims database were consistent with our study, showing higher persistence rates for infliximab as combination therapy with methotrexate.[28] Similar to our study, another US study reported that dose escalation is frequently prescribed in US patients with RA treated with infliximab.[29] Our results are also consistent with earlier studies demonstrating reduced drug persistence among anti-TNF switchers versus first time users.[30]

In contrast to multiple European registry studies, we observed that the disease activity level on anti-TNF initiation in our US-based registry was substantially lower. The majority of both biologically naive and anti-TNF switched patients had low or moderate disease activity at baseline before anti-TNF initiation. In contrast, the mean baseline disease activity (DAS28) in various European RA biological agent registries are consistently greater than 5.1.[3–7 23 31] In fact, these baseline characteristics in the European registries more closely resemble RA patients enrolled in anti-TNF RCT. As demonstrated in our study, drug response

is strongly influenced by the disease activity eligibility criteria routinely applied in RCT. These differences in patient characteristics and dosing patterns between European and US-based RA populations prescribed biological agents may in fact influence comparative effectiveness results, reinforcing the complementary importance of both US and European registries.[23]

Our study has numerous strengths. This study represents one of the largest comparative effectiveness studies of specific anti-TNF agents and anti-TNF switching, derived from a large US-based registry of RA patients with physician-derived outcome measures. We examined three different outcome domains—drug response, remission achievement and persistence on drug—to develop an integrated assessment of drug utilisation and effectiveness of specific anti-TNF agents as well as anti-TNF switching. This work focused on the 'real world' effectiveness of agents in US patients, who are markedly different to RCT subjects in terms of comorbidities and RA disease activity.[12] Our study complements the reports from European registries with improved generalisability to US-based RA patients with lower disease activity and greater access to biological agents. Finally, we were able to examine and adjust for clinical factors that influenced drug response, remission achievement and persistence, as the CORRONA registry prospectively collects these data from the treating rheumatologist at the time of the office visit.

This study also has limitations. Unlike RCT, the timing of the study visits was based on clinic visits, and was requested at intervals of approximately 3 months. Nevertheless, the mean study interval between study visits was approximately 4.5 months, which compares favourably with the intervals reported from the majority of RA registries. In addition, acute phase reactant data were not available for all patients in the study. As a result, we applied previously validated outcome measures not requiring acute phase reactants such as modified ACR outcomes and CDAI remission definition.[17] In fact, the CDAI has recently been shown to be less influenced than the DAS28 by changes in ESR in the normal range, which can inflate remission rates.[32] Finally, given the modest representation of the CORRONA registry relative to the entire US population of RA patients prescribed anti-TNF, there are limitations to the generalisability of our findings.

In conclusion, the results of this US-based study indicate that similar rates of drug response and remission were achieved across the three anti-TNF agents, with more robust effectiveness consistently observed for those who were biologically naive versus patients who switched therapies. Moreover, biologically naive patients prescribed anti-TNF had higher persistence as compared with switchers. Among biologically naive patients, infliximab was associated with greater persistence than the other two agents. Additional comparative effectiveness studies are required to determine if switching to another biological class with a different mechanism of action would improve outcomes compared with intraclass switching strategies. Given the marked differences in disease activity and severity among patients initiating biological agents in the USA versus various European countries, comparative effectiveness studies from both populations are needed to inform their respective patient populations.

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Competing interests JG receives salary support from research grants from the National Institutes of Health (NIH) (K23AR054412), the Arthritis Foundation and the Arthritis National Research Foundation. He serves as chief scientific officer for CORRONA and has served on advisory boards for Centocor, Genentech, and UCB. GR has a research contract with CORRONA. DD is an employee of Janssen Services LLC. LH was supported by grant no K23AR053856 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases. DF receives funding from Abbott, Actelion, Amgen, BMS, BiogenIdec, Centocor, Corrona, Genentech, Gilead, GSK, Human Genome Sciences, Merck, NIH, Nitec, Novartis, Roche, UCB, Wyeth and Xoma. He also serves as director of publications for CORRONA. AG is executive vice president of CORRONA. He is a consultant to Abbott, Amgen, Nicox, Pfizer, Roche, Savient, Takeida and UCB. He is a speaker for Abbott, Amgen, BMS, Pfizer and Roche. In addition, he and/or his spouse are stockholders in Abbott, Amgen, BMS, J&J and Pfizer. RDH is an employee of Centocor Ortho Biotech Services LLP. MK has no competing interests. JMK receives research support from Amgen, Abbott, Centocor, BMS, Genentech, HGS, Pfizer, Roche and UCB as well as honoraria from Abbott, Centocor, BMS, Roche and Genentech.

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A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry

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Use of Hydroxychloroquine in Japan

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Use of Hydroxychloroquine in Japan

To the Editor:

Antimalarial agents have been used for the treatment of inflammatory diseases for the last half century, with hydroxychloroquine (HCQ) being approved in the United States in 1955[1]. In addition to its common use in systemic lupus erythematosus (SLE), including cutaneous forms, it has also proven useful in treating rheumatoid arthritis (RA)[2,3,4] and Sjögren's syndrome[5]. In SLE, antimalarial agents have been shown to decrease disease activity and subsequent flares in both nonpregnant[6] and pregnant patients[7]. Other potential benefits include a decreased risk of infection[8] and thrombosis[9]. HCQ has been shown to exert a positive effect on overall survival[10]. In a large cohort of multiethnic patients with SLE (the LUMINA cohort), HCQ prevented renal and central nervous system disease[11,12]. Finally, a recent report suggests that maternal use of HCQ may decrease the risk of cardiac manifestations of neonatal lupus[13].

Despite these benefits and its current use in over 70 countries, chloroquine and HCQ remain unavailable for clinical use for rheumatology patients in Japan. This unavailability stems from a series of lawsuits in the 1970s as a result of chloroquine retinal toxicity, which was first reported by Cambiaggi in 1957[14] and further confirmed by Hobbs, *et al* in 1959[15]. Interestingly, chloroquine was widely used in Japan for a variety of clinical indications from 1955 through the early 1970s, including malaria, RA, and SLE, as well as in diseases such as epilepsy and chronic nephritis, in which baseline risk of retinal toxicity was likely higher to begin with[16]. The dangers associated with chloroquine use were compounded by the absence of rigorous safety screening protocols, despite the known potential for retinal toxicity. As a result, chloroquine was withdrawn from the Japanese market in 1974.

In the last decade, the clear benefits of antimalarial agents in rheumatological diseases have been increasingly recognized, by the growing cohort of returnee patients already treated with HCQ overseas as well as US-trained rheumatologists returning to Japan for clinical practice. In 2009, an initiative began to promote the study and introduction of HCQ into clinical care in Japan, appreciating the importance of updated safety screening protocols[17,18], including earlier detection of retinal toxicity with newer ophthalmologic modalities such as multifocal electroretinogram, spectral domain optical coherence tomography, or fundus autofluorescence. Given its wide use as a standard of care worldwide, there is little reason to support HCQ's continued absence from the market. Unsurprisingly, a recent small study of HCQ in Japanese patients with SLE showed benefit in cutaneous disease, arthritis, and fatigue[19]. To this end, 2012 will see the first clinical trial of HCQ for SLE in Japan.

We hope that an understanding of the history of antimalarial agents in Japan — a legacy that precluded the appropriate use of an efficacious therapy — will soon lead to an era of improvement of patient care, survival, and quality of life for patients with SLE in Japan.

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Contrast-enhanced whole body joint MR Imaging in rheumatoid patients on tumour necrosis factor-alpha agents: a pilot study to evaluate novel scoring system for MR synovitis

Sirs,

In the past decade the development of biological agents particularly those which target tumour necrosis factor alpha (anti-TNF-α) has started a new era in the management of rheumatoid arthritis (RA). Data from recent studies in patients with RA show that these drugs are very effective in improving clinical and functional outcomes, and have demonstrated the ability to arrest or even reverse radiographic progression (1, 2). In recent years, magnetic resonance imaging (MRI) has increasingly been used as outcome measures in clinical trials of RA (3, 4). Presence of inflammatory involvement of joints other than the hand especially if clinically occult, potentially alter treatment. The aims of the present study were to introduce and describe a novel scoring system for the assessment of whole body joint synovitis, and to assess the relationship with clinical findings in a longitudinal setting in rheumatoid patients treated with anti-TNF-α agents.

The study, which met the requirements of our institutional review board for a retrospective observational study, included 12 consecutive patients (2 men and 10 women; median age, 60 years; age range, 35–73 years) who started anti-TNF-α treatment. The patients had arthritis with a median symptom duration of 55 months (range: 7–276 months), receiving various dose of methotrexate. All patients satisfied the American College of Rheumatology revised 1987 criteria for RA (5) at the time of entry.

Ten patients received intravenous injections of infliximab (Remicade; Tanabe Pharmaceutical, Tokyo, Japan) and 4 patients received etanercept (Enbrel; Amgen, Pfizer/Wyeth, Takeda). The kinds and amounts of other drugs that each patient was taking were not changed during the study period. Each patient was clinically evaluated and underwent MR imaging at baseline and followup. Contrast enhanced MRI was performed on a 1.5T whole body MR system (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany) in a way described elsewhere (6). Briefly, the joints of 13 body regions for each patient: the atlanto-axial joint, bilateral shoulder joints, bilateral wrist joints, bilateral MCP joints, bilateral hip joints, bilateral knee joints, and bilateral metatarsophalangeal (MTP) joints were scanned and evaluated. Image acquisition was started immediately after completing contrast injection and joints were scanned in the order mentioned above. The examination time was less than 30 minutes. The MR images were assessed by one experienced radiologist, who was blinded to all clinical information. Hand joints were evaluated according to RAMRIS for synovitis. Remaining joints were scored in the similar way as RAMRIS for hand joints (7).

Table. Correlation in treatment effect between MR measures and clinical data / disease activity.

	ΔMR-positive joint count			ΔMR synovitis score		
	Total	Hand	Remaining	Total	Hand	Remaining
ΔTJC	0.573*	NS	0.554*	0.620*	NS	0.642*
ΔSJC	NS	NS	0.587*	0.598*	NS	0.647*
ΔVAS	NS	NS	NS	NS	NS	NS
ΔESR (mm/hr)	NS	NS	NS	NS	NS	NS
ΔCRP (mg/dl)	NS	NS	NS	NS	NS	NS
ΔDAS28-ESR	NS	NS	NS	0.576*	NS	NS

Δ (delta) means difference between baseline and follow-up studies. *$p<0.05$.

Both MR-positive joint count and MR synovitis score for hands joints did not correlate with any of the measures for clinical data and disease activity. On the other hand, both MR-positive joint count and MR synovitis score for remaining joints correlated moderately to strongly with some measures for clinical data and disease activity. There was moderate positive correlation between delta MR synovitis score for total joints (hands and remaining joints) and delta DAS28-ESR. Here, delta means the difference between baseline and follow-up studies (Table I).

MR imaging findings of the systemic joints correlate with clinical findings in RA patients, especially when scoring analysis for synovitis is performed. Compared to hand joints, changes in MR synovitis score caused by therapeutic agent such as anti-TNF-α may be more sensitive in remaining joints. This may indicate that images obtained beyond the appropriate time window of 5–10 minutes after contrast injection (8) are useful to evaluate the response to treatment. Although the group of patients studied was small and non homogeneus, this approach may be useful for sensitive analysis of systemic synovitis in rheumatoid patients. Study with a greater number of patients with healthy controls is necessary to obtain more solid conclusions.

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Concise report

Positive synovial vascularity in patients with low disease activity indicates smouldering inflammation leading to joint damage in rheumatoid arthritis: time-integrated joint inflammation estimated by synovial vascularity in each finger joint

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Abstract

Objective. To investigate the relationship between synovial vascularity and joint damage progression in each finger joint of patients with RA under low disease activity during treatment with biologic agents.

Methods. We studied 310 MCP and 310 PIP joints of 31 patients with active RA who were administered adalimumab (ADA) or tocilizumab (TCZ). Patients were examined with clinical and laboratory assessments. Power Doppler sonography was performed at baseline and at weeks 8, 20 and 40. Synovial vascularity was evaluated according to quantitative measurement. Hand and foot radiography was performed at baseline and at week 50.

Results. Composite scores of the DAS with 28 joints and the Simplified Disease Activity Index (SDAI) were significantly decreased from baseline to week 8, being sustained at a low level by biologic agents during the observational period. MCP and PIP joints with positive synovial vascularity after week 8 showed more subsequent joint damage progression than joints without synovial vascularity throughout the follow-up. The changes in radiographic progression in these joints were independent of the sum of synovial vascularity from baseline to week 40 or the occasional occurrence of positive synovial vascularity.

Conclusion. Smouldering inflammation reflected by positive synovial vascularity under low disease activity was linked to joint damage. The damage progressed irrespective of the severity of positive synovial vascularity. Even with a favourable overall therapeutic response, monitoring of synovial vascularity has the potential to provide useful joint information to tailor treatment strategies.

Trial registration. University Hospital Medical Information Network Clinical Trials Registry; http://www.umin.ac.jp/ctr/: UMIN000004476.

Key words: rheumatoid arthritis, power Doppler sonography, synovial vascularity, low disease activity.

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Introduction

In RA, clinical evaluations for disease activity such as patients' symptoms, joint examinations and laboratory data do not have enough power to provide details on local joint inflammation [1]. To assess rheumatoid disease activity, composite scores such as the ACR core data set or the DAS with 28 joints (DAS28) have been developed to

compensate for the weak points in the use of a single clinical marker [2, 3]. Although these composite scores have been well established as disease activity markers, they cannot precisely predict the destruction of individual joints.

The appearance and increase in synovial vascularity related to vasodilation and angiogenesis indicates active joint inflammation [4]. Power Doppler sonography (PDS) enables visualization of synovial vascularity and numerical representation of local inflammation [5, 6].

We focused on the clinical significance of synovial vascularity in RA. We previously reported the prediction of the progression of local finger joint damage via early changes in synovial vascularity [7, 8]. Interestingly, we observed finger joints with persistence of synovial vascularity after achieving low disease activity. Here we report on the relationship between synovial vascularity and joint damage progression in two patient groups treated with different biologic agents, focusing on finger joints with positive synovial vascularity after achieving low disease activity.

Patients and methods

Patients

Thirty-one patients with RA who had started adalimumab (ADA) or tocilizumab (TCZ) therapies were analysed. The patients had been pre-treated with DMARDs [ADA: eight patients with MTX, one with tacrolimus (TAC), one with bucillamine (BUC) + TAC, one with MTX + TAC and one with SSZ + TAC; TCZ: nine patients with MTX, one with BUC and two with TAC] or pre-treated with biologic agents [ADA: one patient with MTX + infliximab (IFX); TCZ: three patients with MTX + IFX, one with MTX + etanercept and two with MTX + ADA]. Despite these treatment histories, all patients were refractory cases having at least one swollen joint in the MCP/PIP joints and a DAS28-ESR > 3.2. Demographic, clinical and laboratory characteristics of the patients are shown in Table 1. After baseline examinations, ADA was given to 13 patients and TCZ to 18 patients. The biologic agents were given according to the standard protocols (ADA 40 mg s.c. injection bi-weekly, TCZ 8 mg/kg i.v. infusion every 4 weeks). This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of Hokkaido Medical Center for Rheumatic Diseases. Informed consent was obtained from all patients before they entered the study.

Clinical examination

Swollen and tender joints and global assessment on a visual analogue scale (VAS) were assessed at baseline and at weeks 8, 20 and 40 by rheumatologists (J.F., M.S., M.M., K.T.) who were blinded to the ultrasonographic results. Blood tests for ESR and CRP were performed at each assessment.

Ultrasonography and assessment

Ultrasonography was performed at baseline and at weeks 8, 20 and 40 by one of three US experts (M.H., F.S., A.N.) specialized in musculoskeletal ultrasonography who were blinded to other clinical information. A linear array transducer (13 MHz) and ultrasonographic machine were used (EUP-L34P, EUB-7500, Hitachi, Tokyo, Japan). Power Doppler settings have been previously described [7, 8]. First to fifth MCP and first to fifth PIP joints were scanned in the longitudinal plane over the dorsal surface. The quantitative PDS method was established in a previous report [8]. A value of synovial vascularity was determined by counting the number of vascular flow pixels in the region of interest.

Radiography and assessment

Plain radiographs of hands, wrists and feet were obtained at baseline and at week 50. Radiological assessments were examined according to the Genant-modified Sharp score (GSS) by a rheumatologist (M.S.) who was blinded to other clinical information [9].

Statistical analysis

Differences of composite parameters were examined using the Student's *t*-test and other data were examined using a non-parametric test (Wilcoxon's signed-rank test and Mann–Whitney U test). Intra- and interobserver reliability of quantitative PDS were estimated by intraclass correlation coefficients (ICCs). The smallest detectable change for the radiographic score change was calculated according to a previous study [10]. $P < 0.05$ indicated statistical significance. Statistical analyses were calculated with the use of Excel (Microsoft, Redmond, WA, USA) and MedCalc 12.1.4.0 (MedCalc Software, Mariakerke, Belgium).

Results

Clinical disease activity

At baseline there were no significant differences of DAS28-ESR and SDAI between the ADA and TCZ groups (Table 1). In both groups these parameters were significantly decreased from baseline to week 8, followed by sustained low disease activity (ADA: $P = 0.0007$, $P = 0.0005$; TCZ: $P < 0.0001$, $P < 0.0001$, respectively) (Table 1).

Radiographic evaluation of joint damage

At baseline there were no significant differences in total GSS (TGSS) between the ADA and TCZ groups (Table 1). In both groups the TGSS increased significantly from baseline to week 50 ($P = 0.0122$, $P = 0.0181$, respectively).

Local GSS (LGSS) was evaluated in each finger joint. In the ADA group the median of the LGSS at baseline for MCP and PIP joints was 2 [interquartile range (IQR) 2–4] and 3 (IQR 1.5–4), respectively, and in the TCZ group the median of the LGSS at baseline for MCP and PIP joints was 3 (IQR 2–4) and 3 (IQR 2–4), respectively. The smallest detectable change values was calculated for the LGSS for single MCP and PIP joints [0.33, 0.31 less than the smallest unit of GSS scoring (0.5)].

TABLE 1 Clinical and laboratory characteristics of patients at baseline

	ADA	TCZ	*P*-value
Age, mean (range), years	53 (24–78)	56.4 (33–77)	0.516
Sex, female/male, *n*	12/1	18/1	
Duration of symptoms, median (IQR), months	62 (11–147)	142 (72–178)	0.156
ESR, median (IQR), mm/h	48 (34–54)	54 (34–64)	0.389
CRP, median (IQR), mg/dl	0.51 (0.09–0.89)	1.31 (0.24–3.03)	0.089
Swollen joint count, median (IQR)	3 (2–5)	5 (3–7)	0.179
Tender joint count, median (IQR)	5 (1–8)	4 (2–9)	0.984
Patient's global assessment by VAS, median (IQR)	50 (42–65)	67 (40–80)	0.544
Examiner's global assessment by VAS, median (IQR)	40 (40–50)	50 (33–70)	0.56
DAS28-ESR (S.D.)			
Baseline	5.03 (1.16)	5.28 (1.08)	0.575
Week 8	2.96 (0.86)	2.93 (0.81)	0.936
SDAI (S.D.)			
Baseline	21 (10.5)	24.7 (11.3)	0.275
Week 8	7.61 (5.48)	8.84 (4.31)	0.60
TGSS, median (IQR)			
Baseline	99.5 (73–116)	122.75 (98.75–160.75)	0.238
Week 50	108.5 (73–134.5)	125 (99.88–164.88)	0.271

Relationship between positive synovial vascularity and radiographic progression in finger joints

In the ADA group the mean and median of local synovial vascularity at baseline for the MCP and PIP joints were 197 and 0 (range 0–3053) and 218 and 0 (range 0–2414), respectively. In the TCZ group the mean and median of local synovial vascularity at baseline for the MCP and PIP joints were 416 and 0 (range 0–4686) and 167 and 0 (range 0–3195), respectively. Local synovial vascularity in both the ADA and TCZ groups decreased significantly from baseline to week 8 (ADA: MCP $P=0.0001$, PIP $P<0.0001$; TCZ: MCP $P=0.0002$, PIP $P=0.004$). We next categorized finger joints into four groups according to the occurrence of patterns of positive synovial vascularity: joints without synovial vascularity throughout the observational period [the negative (N) group], joints with positive synovial vascularity limited to the period from the baseline to week 8 [the therapeutic response (R) group], joints with intermittent occurrence of positive synovial vascularity in the observational period [the intermittently positive (IP) group] and joints with persistent positive synovial vascularity throughout the observational period [the persistently positive (PP) group]. Each patient had a different pattern of joints with positive synovial vascularity: patients in the N group (ADA $n=2$, TCZ $n=2$), patients in the R group (ADA $n=3$, TCZ $n=3$), patients in the IP or PP groups (ADA $n=3$, TCZ $n=6$) and patients in the mixed R and IP or PP groups (ADA $n=5$, TCZ $n=7$).

The change in the LGSS (ΔLGSS) of the R group showed no progression as compared with the N group or showed improvement of joint damage in the PIP joints of the ADA treatment group (Fig. 1). We next focused on the joints with positive synovial vascularity after week 8, comprising the IP and PP groups. These joints showed an increased ΔLGSS as compared with the N group (Fig. 1). The ΔLGSS between the IP and PP groups showed no significant difference with either ADA or TCZ treatment (Fig. 1).

To analyse the relationship between synovial vascularity and ΔLGSS in more detail in the joints comprising the IP and PP groups, we calculated the sum of synovial vascularity of each finger joint from baseline to week 40 to represent the total exposure to inflammation during the treatment period. The medians of the sum of synovial vascularity with ADA therapy for the MCP and PIP joints were 1456 (range 71–6352) and 1136 (range 71–4757), respectively. The medians of the sum of synovial vascularity with TCZ therapy for the MCP and PIP joints were 2947 (range 71–11289) and 1385 (range 71–5964), respectively. We categorized these joints into two groups: those with a sum of synovial vascularity $\leqslant$ median value [the low-level (L) group], and those with a sum of synovial vascularity $>$ median value [the high-level (H) group]. There were no significant differences in the ΔLGSS between the L group and H group with either ADA or TCZ treatment (Fig. 1).

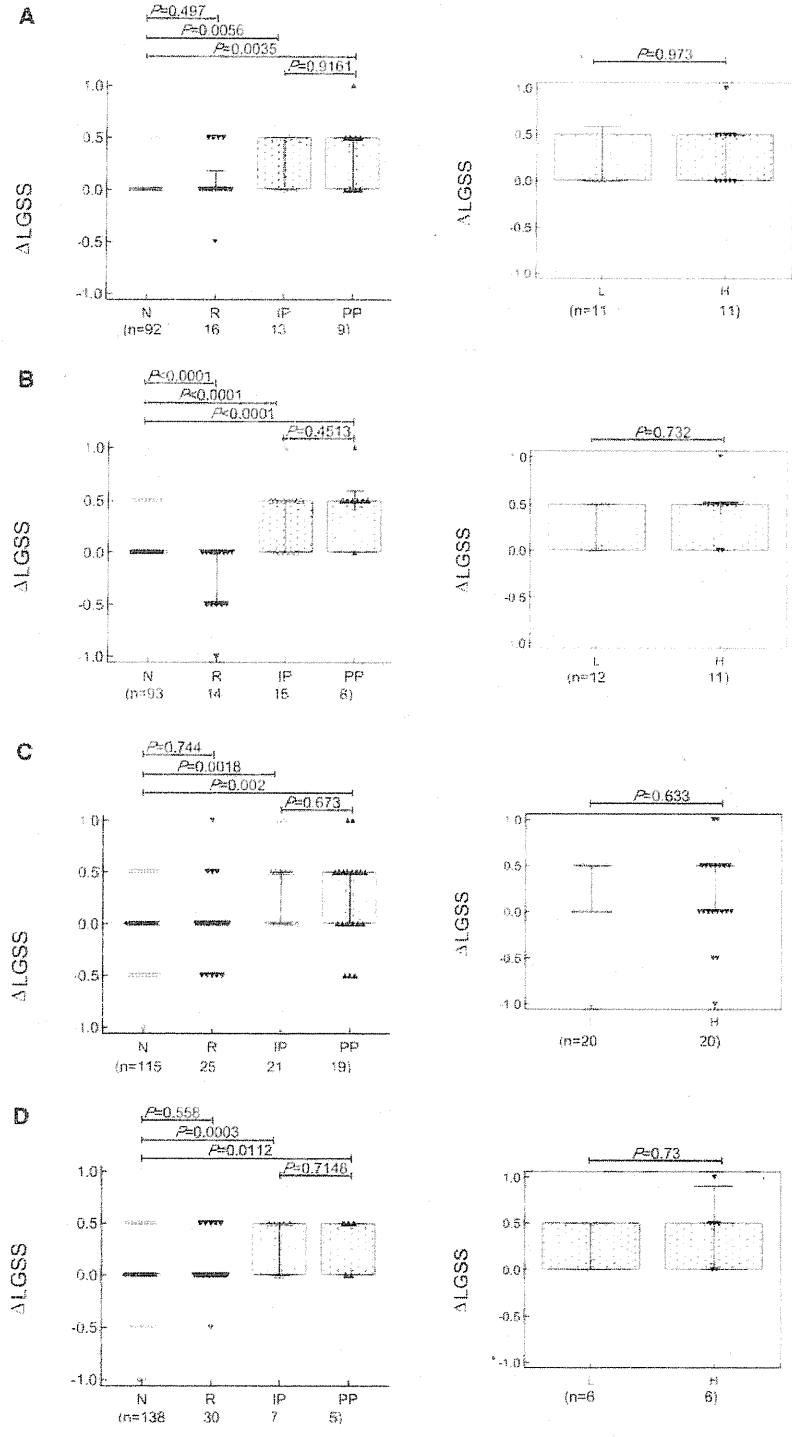
Intra- and interobserver reliability for power Doppler ultrasonography

Representative PDS images for 20 MCP and 20 PIP joints were randomly chosen, and synovial vascularity was measured three times each by the three ultrasonographers (M.H., F.S. and A.N.). The obtained intraobserver ICC values were 0.997–0.999 for MCP joints and 0.998–0.999 for PIP joints. The interobserver ICC values were 0.992–0.996 for MCP joints and 0.991–0.999 for PIP joints.

Discussion

Our study revealed two noteworthy results. First, this study further emphasized a previous report [7] that early improvement and then disappearance of synovial vascularity resulted in reducing joint damage progression.

FIG. 1 Relationship between positive synovial vascularity and LGSS in finger joints.



For ADA treatment. ΔLGSS of MCP (**A**) and PIP joints (**B**) is shown. For TCZ treatment, ΔLGSS of MCP (**C**) and PIP joints (**D**) is shown. Graphs on the left side show ΔLGSS of the N, R, IP and PP groups (Results section), which were categorized according to the occasional occurrence of positive synovial vascularity. For each joint in the IP and PP groups, the sum of synovial vascularity from baseline to week 40 was calculated and then categorized as L and H groups (Results section). Graphs on the right side show ΔLGSS of the L and H groups.

Secondly, a novel result was that persistence of positive synovial vascularity in local finger joints showed joint damage progression despite achieving low disease activity by biologic therapies. Interestingly, the ΔLGSS progressed independently of time-integrated joint inflammation estimated by the sum of synovial vascularity or occasional occurrence of positive synovial vascularity. These joints indicate the presence of low-level local joint inflammation, i.e. smouldering inflammation. The smouldering inflammatory joints could be categorized as a variation of subclinical synovitis described below.

Analysis of RA in the clinical remission phase revealed that there were asymptomatic or symptom-limited joints with poor prognosis. This joint inflammation or so-called subclinical synovitis can only be detected with imaging techniques [11–14]. The growing importance of imaging remission of rheumatoid activity has been confirmed, and imaging techniques such as joint ultrasonography have focused on detailed detection of local joint inflammation [15, 16].

Synovial vascularity detected by PDS is irrefutably linked to the level of joint inflammation [17, 18]. Naredo *et al.* [19] reported the correlation between time-integrated values of joint counts for positive synovial vascularity and total joint damage progression at 1 year. From these results, we speculated that increasing and persistent synovial vascularity might result in advanced joint damage progression; hence an increase in the occasional occurrence of positive synovial vascularity or the sum of synovial vascularity worsens the structural damage in smouldering inflammatory joints. Our data revealed that joints with positive synovial vascularity after week 8 (IP and PP groups) showed joint damage progression; however, their ΔLGSS progression did not relate to the occasional occurrence of positive synovial vascularity or the sum of synovial vascularity (Fig. 1). Accordingly, we concluded that the structural damage in joints with smouldering inflammation progressed independently of the level of the sum of synovial vascularity or the occasional occurrence of positive synovial vascularity. Importantly, the result might indicate that even low levels of positive synovial vascularity that occurred only once during the clinical improvement phase showed a risk for structural damage.

Although a correlation between the progression of systemic joint damage and time-integrated values of joint counts for positive synovial vascularity was reported [19], our study, which focused on synovitis and joint damage in individual finger joints, did not show such correlation. Whereas the previous study [19] showed the effect of non-biologic DMARDs, we studied biologic agents that rapidly improved acute inflammation. The DMARDs have slow therapeutic effect; thus the relationship between exposure to inflammation and joint damage progression may be closer in non-biologic DMARD users. Further, our data showed that some patients were in the mixed R and IP or PP group after starting biologic agents. This might indicate a discrepancy between overall therapeutic response and local joint response. Limitations of our study were its small scale and short observation period. Further larger studies are needed to confirm our observations.

In RA, tight control of joint inflammation is necessary for better outcomes. Treatment strategies should be changed according to the clinical response. Monitoring of synovial vascularity has the potential to provide useful joint information for daily practice and to tailor treatment strategies in RA.

Rheumatology key messages

- Finger joints with positive synovial vascularity under low disease activity showed structural deterioration in RA.
- Monitoring of synovial vascularity has the potential to provide useful information for daily practice in RA.

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