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.

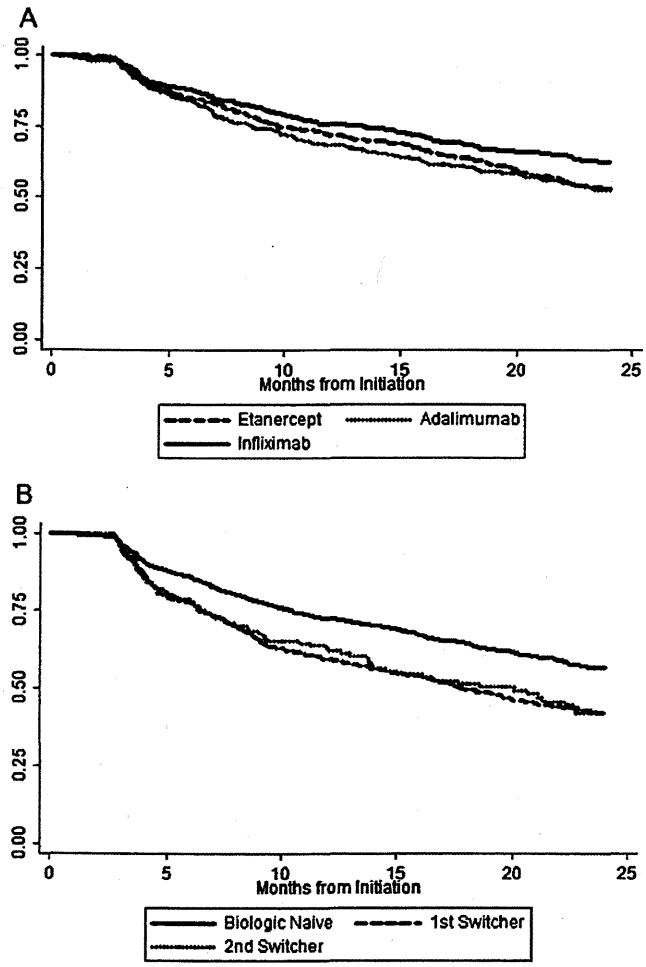

Figure 1 Drug persistency for (A) specific anti-TNF agents in biologically naïve patients and (B) biologically naïve patients versus those switched to anti-TNF agents. TNF, tumour necrosis factor.

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, Biogenldec, 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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REFERENCES

1. **Donahue KE**, Gartlehner G, Jonas DE, *et al.* Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. *Ann Intern Med* 2008;**148**:124–34.
2. **Hochberg MC**, Lebwohl MG, Plevy SE, *et al.* The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. *Semin Arthritis Rheum* 2005;**34**:819–36.
3. **Hetland ML**, Christensen IJ, Tarp U, *et al.* Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum* 2010;**62**:22–32.
4. **Kievit W**, Adang EM, Fransen J, *et al.* The effectiveness and medication costs of three anti-tumour necrosis factor alpha agents in the treatment of rheumatoid arthritis from prospective clinical practice data. *Ann Rheum Dis* 2008;**67**:1229–34.
5. **Erickson AR**, Mikuls TR. Switching anti-TNF-alpha agents: what is the evidence? *Curr Rheumatol Rep* 2007;**9**:416–20.
6. **Hyrich KL**, Lunt M, Watson KD, *et al.* British Society for Rheumatology Biologics Register. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum* 2007;**56**:13–20.
7. **Gomez-Reino JJ**, Carmona L; BIOBADASER Group. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. *Arthritis Rheum* 2007;**56**:13–20.
8. **Karlsson JA**, Kristensen LE, Kapetanovic MC, *et al.* Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. *Rheumatology (Oxford)* 2008;**47**:507–13.
9. HHS.GOV/Recovery. *Text of the recovery act related to comparative effectiveness funding*. Excerpt from the American Recovery and Reinvestment Act of 2009, 2009. http://www.hhs.gov/recovery/programs/cer/recoveryacttext.html (accessed 1 April 2010).
10. The Commonwealth Fund. Use of comparative effectiveness research in drug coverage and pricing decisions: a six-country comparison. http://www.commonwealthfund.org/Publications/Issue-Briefs/2010/Jul/Use-of-Comparative-Effectiveness-Research-in-Drug-Coverage.aspx (accessed 15 Sep 2011).
11. **Siegel J.** Comparative effectiveness of treatments for rheumatoid arthritis. *Ann Intern Med* 2008;**148**:162–3.
12. **Greenberg JD**, Kishimoto M, Strand V, *et al.* Tumor necrosis factor antagonist responsiveness in a United States rheumatoid arthritis cohort. *Am J Med* 2008;**121**:532–8.
13. **Kamal KM**, Madhavan SS, Hornsby JA, *et al.* Use of tumor necrosis factor inhibitors in rheumatoid arthritis: a national survey of practicing United States rheumatologists. *Joint Bone Spine* 2006;**73**:718–24.
14. **Kremer JM**, Gibofsky A, Greenberg JD. The role of drug and disease registries in rheumatic disease epidemiology. *Curr Opin Rheumatol* 2008;**20**:123–30.
15. **Kremer JM.** The CORRONA database. *Ann Rheum Dis* 2005;**64** (Suppl 4):iv37–41.
16. **Kremer JM.** The CORRONA database. *Clin Exp Rheumatol* 2005;**23**(5 Suppl 39):S172–7.
17. **Aletaha D**, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005;**23**(5 Suppl 39):S100–8.
18. **Greenberg JD**, Harrold LR, Bentley MJ, *et al.* Evaluation of composite measures of treatment response without acute-phase reactants in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2009;**48**:686–90.

19. **Goldman JA**, Xia HA, White B, *et al.* Evaluation of a modified ACR20 scoring system in patients with rheumatoid arthritis receiving treatment with etanercept. *Ann Rheum Dis* 2006;**65**:1649–52.
20. **Prevoo ML**, van 't Hof MA, Kuper HH, *et al.* Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:44–8.
21. **Kremer JM**, Greenberg J. Interpreting registry-derived drug studies: does societal context matter? *Arthritis Rheum* 2009;**60**:3155–7.
22. **Bongartz T**, Sutton AJ, Sweeting MJ, *et al.* Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;**295**:2275–85.
23. **Kievit W**, Fransen J, Oerlemans AJ, *et al.* The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. *Ann Rheum Dis* 2007;**66**:1473–8.
24. **Bombardieri S**, Ruiz AA, Fardellone P, *et al.* Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. *Rheumatology (Oxford)* 2007;**46**:1191–9.
25. **Carmona L**, Ortiz A, Abad MA. How good is to switch between biologics? A systematic review of the literature. *Acta Reumatol Port* 2007;**32**:113–28.
26. **Zink A**, Listing J, Kary S, *et al.* Treatment continuation in patients receiving biological agents or conventional DMARD therapy. *Ann Rheum Dis* 2005;**64**:1274–9.
27. **Kristensen LE**, Saxne T, Nilsson JA, *et al.* Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. *Arthritis Res Ther* 2006;**8**:R174.
28. **Tang B**, Rahman M, Waters HC, *et al.* Treatment persistence with adalimumab, etanercept, or infliximab in combination with methotrexate and the effects on health care costs in patients with rheumatoid arthritis. *Clin Ther* 2008;**30**:1375–84.
29. **Stern R**, Wolfe F. Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. *J Rheumatol* 2004;**31**:1538–45.
30. **Gomez-Reino JJ**, Carmona L. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. *Arthritis Res Ther* 2006;**8**:R29.
31. **Hyrich KL**, Lunt M, Dixon WG, *et al.* Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug. *Rheumatology (Oxford)* 2008;**47**:1000–5.
32. **Aletaha D**, Alasti F, Smolen JS. Defining remission in patients receiving tocilizumab is influenced by the choice of the composite index rather than by specific effects on the acute phase response. *Ann Rheum Dis* 2009;**68**(Suppl 3):123.

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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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CONCISE REPORT

Biologic discontinuation studies: a systematic review of methods

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ABSTRACT

Objectives We conducted a systematic review to assess the design and 'failure definition' in studies of biologic discontinuation in rheumatoid arthritis (RA).

Methods We found 403 studies on PubMed, and included nine published papers and five abstracts from scientific meetings. We used a structured extraction form to collect information regarding study design and outcome (failure) definition.

Results Three types of studies were found: randomised controlled trials, long-term extension studies of clinical trials and prospective discontinuation studies. The largest study had 196 subjects in the discontinuation arm. Most studies allowed concomitant use of non-biologic drugs at biologic discontinuation. Heterogeneity was also found in the failure definition. Although all studies used measures of disease activity, the threshold for failure and the time point of assessment differed among studies. Few studies incorporated changing use of non-biologic drugs or glucocorticoids into the failure definition.

Conclusions Although many studies have examined the outcome of biologic discontinuation, they have all been relatively small. Typical practice studies from registries may add important information but will likely need to rely on a broader failure definition.

INTRODUCTION

Aggressive treatment strategies utilising biologic disease-modifying anti-rheumatic drugs (DMARDs) have revolutionised the treatment of rheumatoid arthritis (RA). Remission or low disease activity is now a realistic goal for most patients. After this disease state is achieved, it remains unclear whether biologic DMARDs should be continued indefinitely or discontinued.

Many studies have evaluated biologic discontinuation. However, comparing results from these studies is difficult due to heterogeneous designs and non-uniform definition for failing biologic discontinuation ('failure definition'). Also most studies have focused on RA patients enrolled in biologic trials or standardised protocols, which may not reflect typical practice. To address these issues, rather than focusing on the study results, we evaluated the *study designs* and *outcome (failure) definitions* used in previous studies of biologic discontinuation.

METHODS

Literature search

We conducted a systematic review of the literature. PubMed was searched for the following terms: (rheumatoid OR 'Arthritis, Rheumatoid' [MeSH]) AND (TNF OR 'tumor necrosis factor' OR abatacept OR adalimumab OR anakinra OR certolizumab OR etanercept OR golimumab OR infliximab OR rituximab OR tocilizumab) AND (withdrawal OR discontinuation OR stop). The search period was limited to 1998 (the year when the first biologic DMARD was approved) to 6 April 2013. So that recent studies would be included, abstracts presented at the 2010–2012 meetings of the American College of Rheumatology and the European League Against Rheumatism were also searched. Only material available in English was considered.

The titles of all identified studies were reviewed by one author (KY). The exclusion criteria included (figure 1): studies that did not use biologics, animal or in vitro studies, non-RA studies, reviews without primary data, studies not focusing on the discontinuation of biologic DMARDs, studies that examined biologic discontinuation for side effects, studies that did not report outcomes after biologic discontinuation for good disease control, studies with less than five subjects, paediatric studies, and meeting abstracts without sufficient publicly available details.

Data extraction

Data were extracted for study characteristics We focused specifically on two aspects of the methods: study design and outcome (failure) definition. Each study's study design was assessed for the sample size of the discontinuation arms, study type, the presence of controls who continued biologic DMARDs, focus on early arthritis, requirements before biologic discontinuation, concomitant non-biologic DMARD and glucocorticoid use. We also determined the outcome (failure) definition used to assess failure after biologic discontinuation. This included disease activity thresholds, when and how often the outcome was assessed, and composite failure definition, such as biologic reuse, non-biologic treatment modification and radiographic outcomes. The outcome of the proportion of patients free of failure at 12 months (6 or 7 months' result if 12 months' result was not available) was also described.

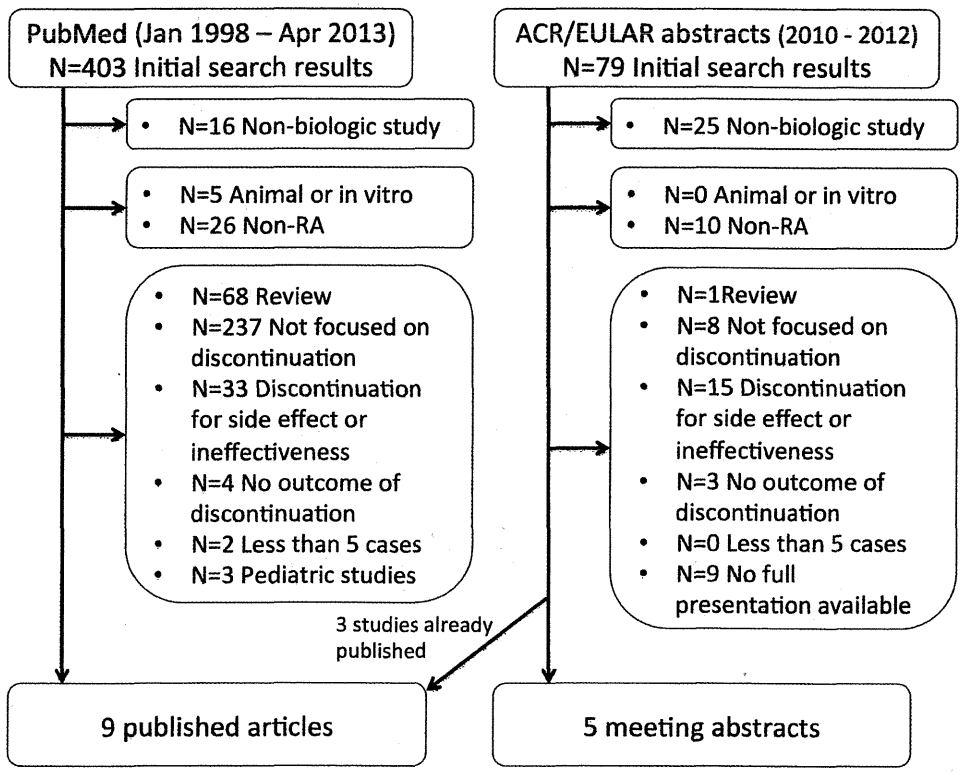

Figure 1 Selection of studies. Literature published after approval of the first biologic disease-modifying anti-rheumatic drug and meeting abstracts in the past 3 years were searched. Steps are explained in the Methods section of the text. ACR, American College of Rheumatology; EULAR, the European League Against Rheumatism; RA, rheumatoid arthritis.

RESULTS

Literature search results

We initially identified 403 abstracts in PubMed (last searched on 6 April 2013). After exclusion criteria were applied (see figure 1), nine studies were considered relevant. Additionally, after exclusion of three published studies, five abstracts had sufficient details to be included, resulting in a total of 14 studies.[1–14]

Study design

The studies were from Europe (n=8),[1 2 5 6 8 10 12 14] Japan (n=4),[3 7 11 13] and the USA and Europe (n=1).[9] The sample sizes in the biologic discontinuation arms varied from 9 to 196. Three types of studies were identified (table 1): randomised controlled trials ('RCT' in table 1),[1 2 5 9] in which discontinuation was randomised; long-term extension of trials ('LTE' in table 1),[3 6 10 14] and single arm prospective studies of discontinuation ('DC study' in table 1)[7 8 11–13] in which patients were prospectively recruited for biologic discontinuation.

Five studies had control arms in which patients with good disease control were kept on biologic treatment.[1–3 5 9] Four studies randomised discontinuation,[1 2 5 9] and three used placebo in place of discontinued biologic treatment and provided at least double blinding.[1 5 9] Four studies focused on early RA patients with less than 1 year of disease,[6 9 10 14] while the other studies were conducted on more established RA patients.

Biologic DMARDs were discontinued after pre-specified duration of use in two studies.[6 14] All other studies used disease activity lower than a specific cut-off as the enrolment criterion. However, the disease activity measures and thresholds varied by study. In one of the studies, biologic discontinuation was assessed as part of a biologic dose reduction protocol,[8] that is, biologic DMARDs were tapered after 6 months of good disease control until discontinuation or failure occurred, and failure of both tapering and discontinuation were reported. Another study had a similar tapering protocol, but only discontinuation was reported.[10] Two studies addressed maintenance treatment with half-dose biologic DMARDs as well as discontinuation.[1 5]

Use of concomitant non-biologic DMARDs and glucocorticoids at the time of biologic discontinuation varied. Some studies required patients to be off glucocorticoids,[7 9 10 13 14] while other studies allowed small doses of glucocorticoids (prednisolone-equivalent, <10 mg/day[1 2 6] or <5 mg/day[11 12]). In general, few details were provided about concomitant treatment in many of the studies.

Outcome (failure) definition

After discontinuation of biologic DMARDs, all RA studies used disease activity thresholds as failure criteria (table 2). The cut-off for failure was either low disease activity or remission, but three studies used a relative definition either by itself[8] or in combination.[2 5] Follow-up duration and time of assessment also varied. Most non-interventional studies (LTE study type) defined failure as an increase in disease activity above the threshold at any time (time to failure analysis), while most interventional studies (RCT and DC studies) assessed disease activity at a pre-specified time,[2 3 5–7 9 14] for example, 6 months after discontinuation.[6]

Biologic DMARD reuse was regarded as failure in all studies except for four studies in which reuse was not allowed.[1 6 9 14] In most studies, reuse was according to protocol, that is, reuse was allowed only after treatment was labelled as failed by the main definition.[2 4 5 7 8 10 12] Treatment changes in non-biologic

Table 1 Comparison of study designs of biologic discontinuation studies

			Design				Discontinuation criteria			Concomitant drugs at discontinuation
Study	Country	Biologic	Sample size*	Study type†	Control group‡	Early RA§	Duration of biologic use	Activity measure	Required duration in good control	DMARDs (%) / glucocorticoids (%)
PRESERVE[1]	Europe	ETN	196	RCT	Yes	No	8 months	DAS28-ESR <3.2	Single time point¶	100/25
ADMIRE[2]	Sweden	ADA	15	RCT	Yes	No	Median 43.3 months	DAS28-ESR <2.6	3 months	100/…
BRIGHT[3]	Japan	ADA	22	LTE	Yes	No	Mean 45.8 months	DAS28-CRP <2.7	Single time point	13.6/40.9
CERTAIN[4]	Europe	CZP	18	LTE	No	No	6 months	CDAI <2.8	1 month	100/…
DOSERA[5]	Europe	ETN	23	RCT	Yes	No	Mean 35.3 months	DAS28-ESR <3.2	11 months	100/…
HIT HARD[6]	Germany	ADA	82	LTE	No	Yes	6 months	None**	NA**	100/…
HONOR[7]	Japan	ADA	51	DC study	No	No	Mean 16.6 months	DAS28-ESR <2.6	6 months	100/0
Van der Maas *et al*[8]	Netherlands	IFX	12	DC study	No	No	Mean 67.2 months	DAS28-ESR <3.2	6 months	68.0/4.0
OPTIMA[9]	USA/Europe	ADA	102	RCT	Yes	Yes	6.5 months	DAS28-CRP <3.2	1 month	100/0
BeSt[10]	Netherlands	IFX	104	LTE	No	Yes	Median 11 months	DAS <2.4	6 months	100/0
RRR[11]	Japan	IFX	114	DC study	No	No	Median 18.5 months	DAS28-ESR <3.2	6 months	100/28.1
Brocq *et al*[12]	France	ADA/ETN/IFX	21	DC study	No	No	Mean 40.3 months	DAS28-ESR <2.6	6 months	67.0/14.3
Nawata *et al*[13]	Japan	IFX	9	DC study	No	No	Median 17.5 months	DAS28-ESR <2.6	6 months	100/0
Quinn *et al*[14]	UK	IFX	10	LTE	No	Yes	12 months	None**	NA**	100/0

*Sample size in the discontinuation arms.
†RCT, randomised controlled trials of discontinuation with continuation controls; LTE, long-term extension of trials; DC study, prospective single-arm studies of discontinuation, in which patients were recruited for biologic discontinuation.
‡Presence of biologic continuation control group.
§Focus on early rheumatoid arthritis mentioned by the authors.
¶DAS28-ESR <3.2 at week 32 and mean DAS28-ESR during weeks 12–32 <3.2 were required.
**Biologic DMARDs were discontinued at 24 weeks and 54 weeks in these studies, regardless of disease activity or duration in good control.
…, no data available; ADA, adalimumab; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; CZP, certolizumab pegol; DAS, Disease Activity Score; DMARDs, disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; ETN, etanercept; IFX, infliximab; NA, not applicable; RA, rheumatoid arthritis.

Table 2 Comparison of outcome (failure) definitions of biologic discontinuation studies

	Main failure definition		Composite failure definition			Outcome
Author	Disease activity measure	Time of assessment* (interval)	Biologic reuse as failure	Non-biologic treatment changes as failure†	x-Ray progression as failure‡	Proportion free of failure§
PRESERVE[1]	DAS28-ESR >3.2	At 12 months	Not allowed	Not allowed	No	42.6% at 12 months
ADMIRE[2]	DAS28-ESR >2.6 or Δ >1.2	At 7 months	Yes¶	...	No	33.3% at 7 months
BRIGHT[3]	DAS28-CRP >2.7	At 12 months	Yes	No	No	18.2% at 12 months
CERTAIN[4]	CDAI >2.8	Within 7 months (...)	Yes¶	...	No	17.6% at 7 months
DOSERA[5]	DAS28-ESR >3.2 and Δ >0.6	At 12 months	Yes¶	Yes	No	13.0% at 12 months
HIT HARD[6]	DAS28-ESR >2.6	At 6 months	Not allowed	Not allowed	No	42.4% at 6 months
HONOR[7]	DAS28-ESR >2.6	Within 12 months (...)	Yes¶	Yes	No	38.3% at 12 months
Van der Maas *et al*[8]	Δ DAS28-ESR >0.6	Within 7 months** (every 2 months+as needed)	Yes¶	No	No	0% at 7 months
OPTIMA[9]	DAS28-CRP >2.6	At 12 months	Not allowed	...	Δ mTSS >0.5/year	43.0% at 12 months
BeSt[10]	DAS >2.4	Within 96 months** (every 3 months)	Yes¶	No	No	80.0% at 12 months
RRR[11]	DAS28-ESR >3.2	Within 12 months (every 1–3 months)	Yes	Yes	Δ mTSS >0.5/year	36.8% at 12 months
Brocq *et al*[12]	DAS28-ESR >3.2	Within 12 months (every month)	Yes¶	Not allowed	No	25.0% at 12 months
Nawata *et al*[13]	DAS28-ESR >2.6	Within 29 months** (...)	Yes	Not allowed	No	44.4% at 12 months
Quinn *et al*[14]	DAS28-ESR deterioration	At 6 and 12 months	Not allowed	...	No	70.0% at 12 months

*Assessment for failure 'at' pre-specified time points or any time 'within' the follow-up duration (survival analysis). Assessment interval is indicated in a parenthesis for 'within'-type studies.
†Treatment modification of non-biologic disease-modifying anti-rheumatic drugs and glucocorticoid at the discretion of the treating physician as part of composite failure definition.
‡x-Ray progression as part of composite failure definition.
§Defined at 12 months (6 or 7 months if 12 months' result is not available). As discussed throughout the article, these results are obtained by different outcome definitions.
¶Biologic DMARD reuse was according to protocol, that is, reuse was allowed only after treatment was labelled as failed by disease activity criteria.
**Follow-up duration varied.
..., no data available; Δ, change in disease activity; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, disease Activity Score; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; mTSS, modified total Sharp score.

treatments at the discretion of the treating physician (increased doses or new introduction of non-biologic DMARDs and glucocorticoids) were used as failure definition in some studies,[5 7 11] but only two studies reported changes in these treatments in detail.[3 8] Two studies used radiographic progression as part of the failure definition,[9 11] although the cut-offs chosen may be arguable considering they were lower than the general smallest detectable differences between readers.[15]

The actual outcomes of the studies varied widely (table 2).

DISCUSSION

We reviewed studies on biologic discontinuation to examine their designs. We found heterogeneity across studies, particularly in study design and outcome (failure) definition. Study enrolment was usually based on disease activity lower than a given threshold, but this threshold differed across studies. The failure definition was consistent in primarily using disease activity measures. However, concomitant non-biologic treatment at discontinuation and treatment changes after discontinuation were not sufficiently reported in most of the studies, and few clearly defined changes in non-biologic treatments as failure. The 'success rates' during the first year varied from 0% to 80%, supporting the substantial heterogeneity noted as regards study methods. In fact, this is precisely why we focused this systematic review on study methods and not on results. While we believe the results of these studies to be very important, the methods need critical appraisal before how the results should be appropriately interpreted is considered.

To collect comparable information, the use of standardised enrolment and failure definition is essential. It is only very recently that RCTs which include biologic continuation control arms have been presented. These are very useful for studying the comparative effectiveness of biologic discontinuation in comparison with biologic continuation. However, such trials apply strict inclusion criteria, creating study cohorts that may not be generalisable. Thus, observational data from registries of typical practice could potentially contribute more clinically relevant information.

There are particular obstacles to registry studies. An increase in disease activity may occur between study visits but not be present at the subsequent study visit, making it difficult to define 'failure' only by disease activity at study visits. This 'interval failure' issue may be partly addressed by including treatment modification as part of composite failure definition (disease activity increase *or* treatment modification as failure). This approach is in agreement with the preliminary consensus definition of RA flare proposed by OMERACT, which described flare as an increase in disease activity that results in treatment modification.[16] However, as there is no consensus on what treatment changes should be considered clinically significant, there is inherent subjectivity in this definition.

In conclusion, the currently available studies show heterogeneity in designs, and suggest need for standardised definitions of biologic discontinuation in good disease control and failure of biologic discontinuation. Standardised failure definition incorporating changes in treatments in addition to the main criteria by disease activity may allow information from currently available clinical practice registries to be utilised, thereby providing information more relevant to typical clinical practice.

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REFERENCES

1 Smolen JS, Nash P, Durez P, *et al*. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 2013;381:918–29.
2 Chatzidionysiou K, Turesson C, Teleman A, *et al*. A multicenter, randomized, controlled, open-label pilot study of the feasibility of discontinuation of adalimumab in rheumatoid arthritis patients in stable clinical remission [abstract]. *Arthritis Rheum* 2012;64(Suppl 10):S336.
3 Harigai M, Takeuchi T, Tanaka Y, *et al*. Discontinuation of adalimumab treatment in rheumatoid arthritis patients after achieving low disease activity. *Mod Rheumatol* 2012;22:814–22.
4 Smolen JS, Emery P, Ferraccioli G, *et al*. Maintenance of remission in rheumatoid arthritis patients with low-moderate disease activity following withdrawal of certolizumab pegol treatment: week 52 results from the CERTAIN study. *Ann Rheum Dis* 2012;71(Suppl 3):361.
5 Van Vollenhoven R, Østergaard M, Leirisalo-Repo M, *et al*. In rheumatoid arthritis patients with stable low disease activity on methotrexate plus etanercept, continuation of etanercept 50 mg weekly or 25 mg weekly are both clinically superior to discontinuation: results from a randomized, 3-armed, double-blind clinical trial [abstract]. *Arthritis Rheum* 2012;64:4171.
6 Detert J, Bastian H, Listing J, *et al*. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* 2013;72:844–50.
7 Tanaka Y, Hirata S, Fukuyo S, *et al*. Discontinuation of adalimumab without functional and radiographic damage progression after achieving sustained remission in patients with rheumatoid arthritis (the HONOR study): 1-year results [abstract]. *Arthritis Rheum* 2012;64(Suppl 10):345.
8 Van der Maas A, Kievit W, Van den Bemt BJF, *et al*. Down-titration and discontinuation of infliximab in rheumatoid arthritis patients with stable low disease activity and stable treatment: an observational cohort study. *Ann Rheum Dis* 2012;71:1849–54.
9 Kavanaugh A, Emery P, Fleischmann RM, *et al*. Withdrawal of adalimumab in early rheumatoid arthritis patients who attained stable low disease activity with adalimumab plus methotrexate: results of a phase 4, double-blind, placebo-controlled trial. *Rheumatology (Oxford)* 2012;51(Suppl 3):iii27.
10 Van den Broek M, Klarenbeek NB, Dirven L, *et al*. Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: subanalysis of the BeSt study. *Ann Rheum Dis* 2011;70:1389–94.
11 Tanaka Y, Takeuchi T, Mimori T, *et al*. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. *Ann Rheum Dis* 2010;69:1286–91.
12 Brocq O, Millasseau E, Albert C, *et al*. Effect of discontinuing TNFalpha antagonist therapy in patients with remission of rheumatoid arthritis. *Joint Bone Spine* 2009;76:350–5.
13 Nawata M, Saito K, Nakayamada S, *et al*. Discontinuation of infliximab in rheumatoid arthritis patients in clinical remission. *Mod Rheumatol* 2008;18:460–4.
14 Quinn MA, Conaghan PG, O'Connor PJ, *et al*. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;52:27–35.
15 Bruynesteyn K, Van der Heijde D, Boers M, *et al*. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. *Arthritis Rheum* 2002;46:913–20.
16 Bartlett SJ, Hewlett S, Bingham CO III, *et al*. Identifying core domains to assess flare in rheumatoid arthritis: an OMERACT international patient and provider combined Delphi consensus. *Ann Rheum Dis* 2012;71:1855–60.

ARD

Biologic discontinuation studies: a systematic review of methods

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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).

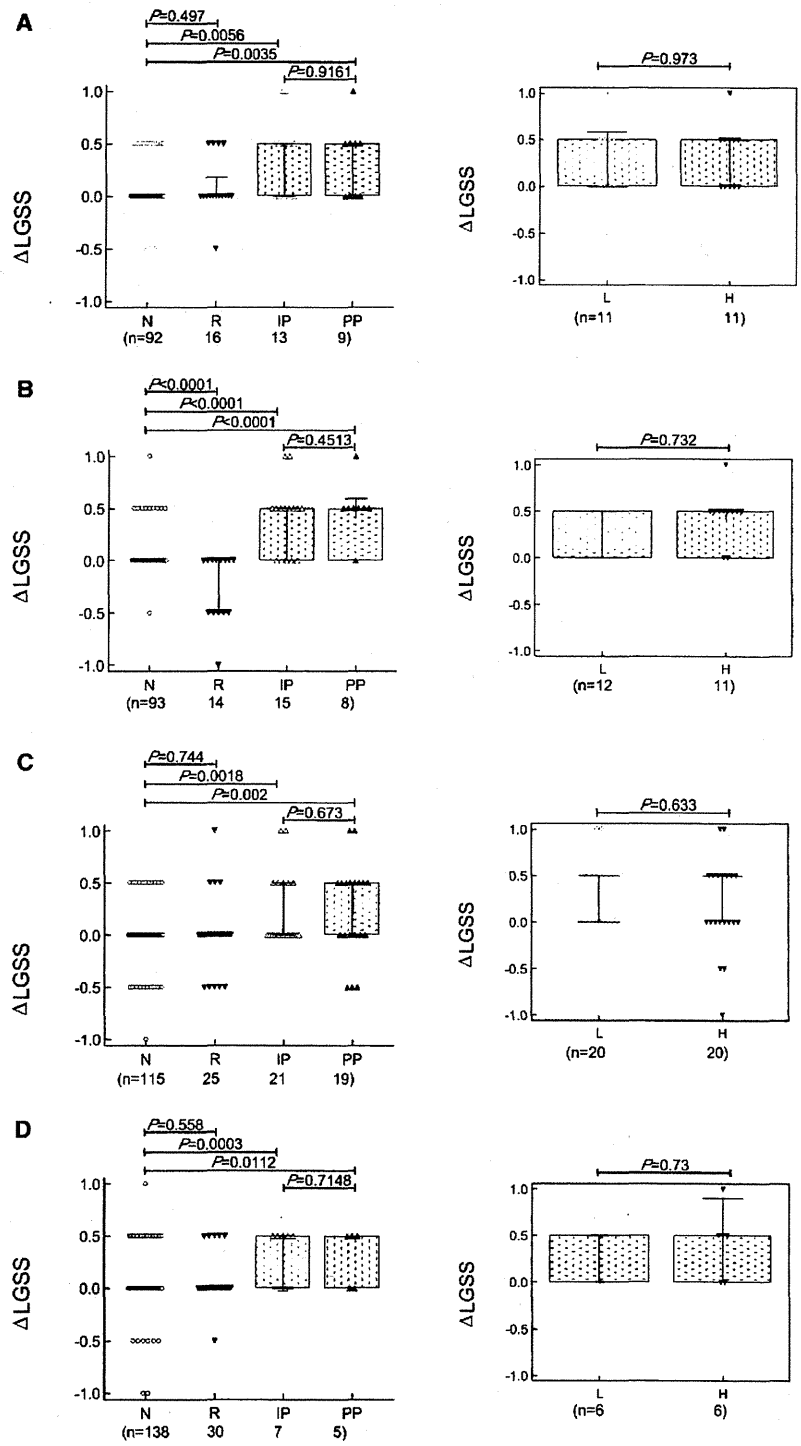
Intra- and interobserver reliability for power Doppler ultrasonography

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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References

1 Jousse-Joulin S, d'Agostino MA, Marhadour T *et al.* Reproducibility of joint swelling assessment by sonography in patients with long-lasting rheumatoid arthritis (SEA-Repro study part II). J Rheumatol 2010;37:938–45.

2 Felson DT, Anderson JJ, Boers M *et al.* Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.

3 Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.

4 Koch AE. Review: angiogenesis: implications for rheumatoid arthritis. Arthritis Rheum 1998;41:951–62.

5 Newman JS, Adler RS, Bude RO, Rubin JM. Detection of soft-tissue hyperemia: value of power Doppler sonography. AJR Am J Roentgenol 1994;163:385–9.

6 Naredo E, Moller I, Cruz A, Carmona L, Garrido J. Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. Arthritis Rheum 2008;58:2248–56.

7 Fukae J, Isobe M, Kitano A *et al.* Radiographic prognosis of finger joint damage predicted by early alteration in synovial vascularity in patients with rheumatoid arthritis: potential utility of power Doppler sonography in clinical practice. Arthritis Care Res 2011;63:1247–53.

8 Fukae J, Kon Y, Henmi M *et al.* Change of synovial vascularity in a single finger joint assessed by power Doppler sonography correlated with radiographic change in rheumatoid arthritis: comparative study of a novel quantitative score with a semiquantitative score. Arthritis Care Res 2010;62:657–63.

9 Genant HK, Jiang Y, Peterfy C, Lu Y, Redei J, Countryman PJ. Assessment of rheumatoid arthritis using

a modified scoring method on digitized and original radiographs. Arthritis Rheum 1998;41:1583–90.

10 Bruynesteyn K, Boers M, Kostense P, van der Linden S, van der Heijde D. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. Ann Rheum Dis 2005;64: 179–82.

11 Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann Rheum Dis 2011;70: 172–5.

12 Brown AK, Quinn MA, Karim Z *et al.* Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum 2006;54: 3761–73.

13 Filippucci E, Iagnocco A, Meenagh G *et al.* Ultrasound imaging for the rheumatologist VII. Ultrasound imaging in rheumatoid arthritis. Clin Exp Rheumatol 2007; 25:5–10.

14 Brown AK, Conaghan PG, Karim Z *et al.* An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008;58:2958–67.

15 Saleem B, Brown AK, Keen H *et al.* Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. Ann Rheum Dis 2011;70:792–8.

16 Dougados M, Devauchelle-Pensec V, Ferlet JF *et al.* The ability of synovitis to predict structural damage in rheumatoid arthritis: a comparative study between clinical examination and ultrasound. Ann Rheum Dis 2012. Advance Access published on 7 June 2012, doi:10.1136/annrheumdis-2012-201469.

17 Schirmer M, Duftner C, Schmidt WA, Dejaco C. Ultrasonography in inflammatory rheumatic disease: an overview. Nat Rev Rheumatol 2011;7:479–88.

18 Lainer-Carr D, Brahn E. Angiogenesis inhibition as a therapeutic approach for inflammatory synovitis. Nat Clin Pract Rheumatol 2007;3:434–42.

19 Naredo E, Collado P, Cruz A *et al.* Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. Arthritis Rheum 2007;57:116–24.

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Sonographic synovial vascularity of synovitis in rheumatoid arthritis

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Abstract

RA is a condition of multiple synovitis. Abnormal synovial vascularity (SV) is evident with the onset of joint inflammation. The idea of estimating the level of joint inflammation by sonographic SV was conceived with the advancement of US. The ideal treatment strategy, called treat to target (T2T), requires early diagnosis and assessment of RA. Detection of positive SV can be useful for proving the presence of synovitis and finally diagnosing RA. In the assessment of RA, US-based global scores aimed at assessing overall disease activity have the potential to be useful for the achievement of T2T because US can directly detect changes in synovitis. Remaining SV in local joints increases the risk of structural deterioration. RA requires both improvement of overall disease activity and the disappearance of local SV for remission. The evaluation of SV provides various information and contributes to the clinical treatment of RA.

Key words: rheumatoid arthritis, ultrasound, power Doppler sonography, synovitis, synovial vascularity, treat to target.

Introduction

Today, why are rheumatologists enthusiastic to evaluate synovial vascularity (SV) in patients with RA in daily practice? RA is a condition of multiple cryptogenic synovitis characterized by expansion of soft tissue and destructive bone invasion at various joint sites that results in systemic musculoskeletal dysfunction. The pathogenesis of rheumatoid synovitis has been strongly associated with SV (Fig. 1).

Pathological explorations have tried to discover the characteristic pathogenesis of rheumatoid synovitis, and in recent years it has become apparent that with the onset of inflammation, abnormal vascularization is evident in the synovium due to vasodilation or angiogenesis [1–5]. A close relation between SV and synovitis has been confirmed. Presently SV is one of the hottest topics in rheumatology clinics.

Various factors such as the variety of afflicted joint sites or the diversity of disease progression may affect evaluation of the disease activity of RA. Composite scoring, which comprises clinical findings such as tender or swollen joint counts, has been established to evaluate the overall disease activity of RA. Clinical composite scores such as the 28-joint DAS (DAS28), the Simplified Disease Activity Index and the Clinical Disease Activity Index have been proven to be useful by various clinical trials [6, 7]. Although these clinical composite scores assess overall disease activity, they do not satisfactorily alert the clinician to changes in local joints due to their dichotomous judgment for each joint. To achieve deep remission of RA and to halt all abnormal joint destruction, the focus must be on detecting changes in local joint inflammation.

Progress in digital technology has resulted in US systems that produce high-quality images that enable observation of small joints. The novel idea of estimating the level of joint inflammation by sonographic SV was conceived with advancements in power Doppler US (PDS). Newman *et al.* [8, 9] first reported the use of PDS to detect abnormal SV, and Szkudlarek *et al.* [10] compared PDS with dynamic MRI to assess synovitis in finger joints and showed equivalency with both techniques.

With advancements in treatments for RA, early diagnosis and treatment have come to the forefront [11–14]. In response to this, new ACR/ European League Against Rheumatism (EULAR) classification criteria were introduced in 2010 [15, 16]. These criteria specify that patients with probable synovitis are first screened according to

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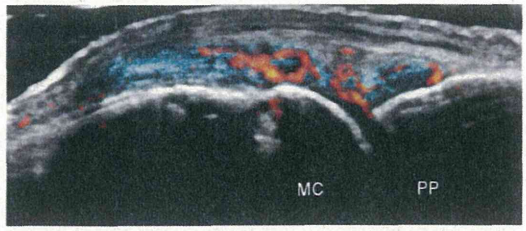
FIG. 1 Longitudinal US image of a metacarpophalangeal joint in a patient with RA.



The multicolour fusion image of grey-scale and corresponding power Doppler images shows inflamed hypertrophic synovial tissue digitally stained in blue and abnormal SV stained in red. MC: metacarpal head; PP: proximal phalanx.

clinical findings. SV reflects the presence of synovitis in the early stage with high specificity.

Here we review the potential of SV detected by PDS for use in the diagnosis and assessment of RA.

Assessment of SV

PDS is essentially a flexible and sonographer-dependent examination. Although PDS is useful for the assessment of SV, reproducibility is a major problem [17]. Settings of US machines and the scanning technique of the sonographer can greatly influence the visualization of SV, which affects reproducibility. Among the various US machine settings, US parameters such as pulse repetition frequency influence the quality of PDS imaging. Further, deterioration of the US transducer can adversely affect PDS imaging. Thus appropriate machine settings and maintenance are critical to ensure stable and reproducible PDS imaging. To minimize problems of the scanning technique, standardization of joint scanning has been studied by the EULAR [18, 19]. Education of the sonographer and proficiency in scanning are important for stable PDS imaging and improves reproducibility.

To measure SV by PDS, a semi-quantitative scoring system has been described [20] that comprises four scoring categories (0, none; 1, mild; 2, moderate; 3, severe) determined by the area of SV and grossly scored from the PDS images. This simple method has the advantage of no requirement for additional devices or special software, but reproducibility and reliability are problematic. Several clinical trials, most performed by members of the EULAR, have addressed these issues [21–24]. These studies found that appropriate training in scanning technique and reading of PDS images could improve and stabilize the reproducibility and reliability of scoring. However, this semi-quantitative scoring system might not be satisfactory to assess joint inflammation because it includes only four scoring categories. Therefore quantitative methods were established to measure SV in more detail [25–27]. Several groups reported a quantitative method to measure pixel counts of SV in the region of interest, which was located at in synovial tissue. Quantitative measurement could show the level or changes of SV numerically.

Because US is fundamentally a two-dimensional (2D) assessment, the images reflect a cross section of volumetric synovial tissue. Therefore the question of a discrepancy between sonographic assessment and the level of practical inflammation always exists. Recently three-dimensional (3D) PDS has been developed that enables assessment of SV at a volumetric level [28, 29]. This method may have several advantages, including image reproducibility and fewer training requirements for scanning joints or reading images. Naredo *et al.* [30] reported that 3D PDS showed repeatability such that it could be used in multicentre cohort studies of RA.

Abnormal SV in the early diagnosis of RA

Because abnormal SV is strongly associated with the pathology of synovitis, logically, detecting abnormal SV at symptomatic joints may be useful for proving the presence of synovitis and in finally diagnosing RA. We previously reported that when the sum of the levels of SV at the finger joints in each undiagnosed patient exceeded a certain level, the patient was ultimately diagnosed as having RA [31]. This result indicated the potential for detection of SV to become a first-stage screening test for RA. Importantly, diagnosis of RA requires not only detection of synovitis, but also systemic evaluation including serological or clinical tests.

The new 2010 ACR/EULAR classification criteria for RA were introduced with the aim of diagnosing RA earlier than with conventional methods [15, 16]. Attempts to combine the 2010 ACR/EULAR classification criteria with detection of synovitis by US to improve diagnostic power were reported from several groups [32–34]. Kawashiri *et al.* [33] reported that positive signs of sonographically abnormal SV in patients with undefined arthritis were a stronger prognostic factor for developing RA than were MRI findings or the presence of sonographic synovial hypertrophy. Nakagomi *et al.* [34] reported that US findings, including positive SV, had the power to confirm the presence of synovitis and increased the accuracy of the classification criteria. Thus, in the early diagnosis of RA, detection of abnormal SV has the potential to be used as a screening test or to confirm clinical findings.

Change in SV for assessment of overall disease activity in RA

Estimation of SV can be useful for assessment of disease activity in RA [35]. Although the semi-quantitative scoring system comprises only four categories, and thus is inadequate to assess changes in local joints, it could be useful for assessment of overall disease activity in combination with US estimation at several joints. US-based global scores aimed at assessing overall disease activity consist of the synovial hypertrophy score and SV score. These