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EXTENDED REPORT

What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review

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ABSTRACT

Objective Initiation of DMARD-therapy in the 'window of opportunity' is thought to result in a more effective modification of the processes underlying rheumatoid arthritis (RA). We questioned whether this effect is true or hyped and performed a systematic literature review.

Methods Medical literature databases up to June 2012 were systematically reviewed for cohort studies and randomised controlled trials reporting outcome data of early RA in relation with symptom duration at treatment initiation. The quality of these studies was assessed by two independent reviewers using a criteria scoring system of 15 items. Studies were dichotomised with the median score (79%) as cut-off. Best-evidence synthesis was applied to determine the level of evidence per outcome category. A meta-analysis was performed on the studies reporting on achieving DMARD-free sustained remission (the reverse of disease persistency).

Results Out of 836 screened articles, 18 fulfilled the selection criteria and were not duplicates. Ten were scored as high quality. Remission (various definitions) and radiographic progression were frequently studied outcomes. There was strong evidence for an association between symptom duration and radiographic progression. A meta-analysis on datasets evaluating DMARD-free sustained remission showed that symptom duration was independently associated with such remission; HR 0.989 (95% CI 0.983 to 0.995) per week increase in symptom duration. A moderate level of evidence was observed for other remission outcomes.

Conclusions Even when heterogeneity of patients is taken into account, prolonged symptom duration is associated with radiographic progression and a lower chance on DMARD-free sustained remission. These data may support the presence of a 'window of opportunity'.

INTRODUCTION

Delay in initiating treatment after the diagnosis rheumatoid arthritis (RA) has been established is associated with progression of joint damage.[1] Recently it has been suggested that it is important to initiate treatment even earlier, in the so-called therapeutic 'window of opportunity'.[2] Although not yet fully understood, this window is said to represent a very early phase in the disease in which therapeutic disease modification is more successful, presumably because of not fully matured underlying disease processes. The thought is that intervention in this period may hamper disease progression in such a way that chronicity is reduced. In case such a period is present, this has important consequences for the care of RA, as using this period will reduce the burden of the disease and may, for instance, reduce the number of patients who ultimately require biologics. If a period in which the disease is more susceptible to disease modifying drugs truly exists, efforts resulting in identification of a very early stage of RA may also be cost effective.

However, the question arises; does it really exist? One reason for advocating an absence of this particular window is citation bias, assuming that positive studies are preferentially cited and those with negative results neglected. Since many studies have included symptom duration as covariate in their analysis, it is relevant to systematically review all such studies in order to assess whether short symptom duration at treatment initiation is associated with less progression of the disease.

It has also been suggested that the window of opportunity encompasses the first 12 weeks after symptom onset.[3 4] A difficulty here is that the definition of symptom onset is highly variable between studies[5]; it can relate to the start of symptoms or the start of swelling, and be self-reported by patients or recorded by physicians. Such differences yield incompatibility between studies with regard to the timeframe that was assessed, and preclude performing an extensive meta-analysis. We therefore aimed to perform a qualitative systematic literature review, focusing on two outcomes of early RA; achieving remission and the severity of radiographic joint damage progression.

METHODS

Identification of studies

To identify studies investigating the relationship between symptom duration and the outcome of RA, we searched with the assistance of a medical librarian (JS) in medical literature databases (MEDLINE (OVID-version), PubMed, Embase (OVID_version), Web of Science, CochraneLibrary, CINAHL, Academic Search Premier and ScienceDirect) up to June 2012. Central terms in our analysis were 'RA' and 'symptom duration', for a detailed overview of the search per database, please see online supplementary file 2. Additional articles were searched in the reference lists of identified articles or via expert opinion.

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Inclusion and exclusion criteria

Selection of titles, abstract and articles was performed independently by two reviewers (JABvN and AHMvdH-vM). In case of disagreement, consensus was reached after discussion. First, all retrieved titles were screened, subsequently, abstracts were retrieved for detailed review and, finally, full text articles were read and screened on our inclusion/exclusion criteria.

Included studies fulfilled the following criteria: (1) patients with RA were studied, (2) patients were prescribed DMARDs, allowing to evaluate the time period before treatment initiation, (3) patients had early disease; symptom duration (period between symptom onset and start of treatment) was recorded and <2 years, (4) patients were followed prospectively and follow-up was ≥1 year and (5) symptom duration was part of the analyses on disease outcome.

Animal studies, studies with patients <18 years, reviews, (conference) abstracts, letters to the editor, case reports, case series and studies in languages other than English were excluded.

Data extraction

A standardised form was used to extract information about the following data: (1) study population (population size, setting and time period of the study, symptom duration, age and gender), (2) follow-up period, (3) outcomes (joint damage progression, remission or other outcomes), (4) effect estimates.

Methodological quality assessment

The quality of each included paper was reviewed by two reviewers independently (JABvN and AHMvdHvM) using a maximum of 15 criteria (see online supplementary table S1), which were based on previous systematic reviews in the field of musculoskeletal disorders.[6 7] The criteria were adapted for our research question of symptom duration. When a criterion was met in the article, a '1' was given, otherwise a '0'. A '0' was also given when no information was given about the specific criterion mentioned in the article. In case of differences in ranking, a consensus was agreed after discussion. The maximum score (100%) for each study was based only on the items that were applicable for that study design (randomised controlled trial with radiographic outcome 15, and 14 without, observational cohort with radiographic outcome 14, and 13 without). Total scores per study were calculated as the percentage of maximum obtainable scores.

Rating level of evidence

Because the studies obtained were heterogeneous with regard to the reported effect estimates, a pooled-effect estimate could not be calculated (except for a meta-analysis on the outcome achieving DMARD-free sustained remission). Therefore, we performed a best-evidence synthesis based on the guidelines on systematic review of the Cochrane Collaboration Back Review Group.[8] This is a method to summarise evidence in observational studies if the population, outcomes and data analyses are heterogenic. It consists of five levels of evidence (table 1). A study was considered to be of high quality (HQ) if the total quality score was ≥79% (which is the median of the quality scores obtained in this study).

Table 1 Best evidence synthesis used in this article

Strong	Generally consistent findings (≥75%) in multiple high-quality longitudinal studies
Moderate	Generally consistent findings (≥75%) in multiple low-quality longitudinal studies and/or positive findings in one high-quality longitudinal study
Limited	Findings in one or more low-quality longitudinal studies
Conflicting	Inconsistent findings among multiple longitudinal studies
No evidence	No longitudinal studies, either observational cohorts or RCTs, could be found

RCT, randomised controlled trial.

Data analysis

Three studies reported on the same outcome (achieving a DMARD-free sustained remission) and were homogeneous in the definition of symptom onset (by the patient reported start of symptoms).[9–11] The data of these three datasets were evaluated with univariable and multivariable Cox regression analyses. An inverse weighted meta-analysis on these datasets was performed; the effect estimate was the HR. A fixed-effect model was used. The follow-up durations of these datasets, as reported in the articles, were 10 years[9 10] and 5 years.[11] STATA V.12 was used.

RESULTS

Selection and inclusion of articles

In total, 1625 titles were identified; after removing duplicate references, 836 unique references were left for screening (see figure 1). After detailed review, 22 articles satisfied the inclusion and exclusion criteria.[9–30] Four of these were excluded, since they concerned duplicate patient populations (two were based on the Leiden Early Arthritis Clinic,[20 29] one publication on the BeSt trial[19] and one publication on the FINRACo trial[26]). Consequently, in total, 18 articles were used for further analyses (see table 2).

Methodological quality assessment

The two reviewers scored 249 items in total and agreed on 234 items (94%, table 2), the 16 disagreements were resolved in consensus (see online supplementary table S1). The median quality score was 79% (mean 72.7%, range 43–100%). Consequently, articles with scores ≥79% were ranked as HQ. Low-quality (LQ) studies frequently missed points on the following items: description of the source population and information on the accurateness of determined outcomes. Additionally, few studies assessed the presence and consequences of lost to follow-up.[9 10 16 21 22 30] Finally, of all included studies, information on the definition of symptom onset was provided in only 28%.[9 10 16 21 30]

Study characteristics

The characteristics of the 18 included studies are shown in table 3. The majority of the patients were female and, generally, patients were aged >50 years. In all studies, RA was classified according to the 1987 American College of Rheumatology (ACR) classification criteria, except for one study that used the diagnosis of the rheumatologist.[22] The number of patients included varied between 40 and 895. Frequencies of symptom duration were reported in different ways; mean±SD, median (IQR) or percentages (table 3). Various outcome measured were assessed; the majority related to radiographic joint damage or remission, though actual measures were variable. Progression of radiographic joint destruction was measured using the Larsen score (n=4), the Sharp–van der Heijde score (SHS) (n=4), the Sharp score (n=1) or the presence/absence of erosiveness (n=1). Remission was defined as a state after treatment (eg, Disease activity score (DAS)-28<1.6, DAS-28<2.6, DAS-44<1.6, ACR-remission (n=1, n=2, n=1 and n=2, respectively)), or as the resolution of disease persistency, which

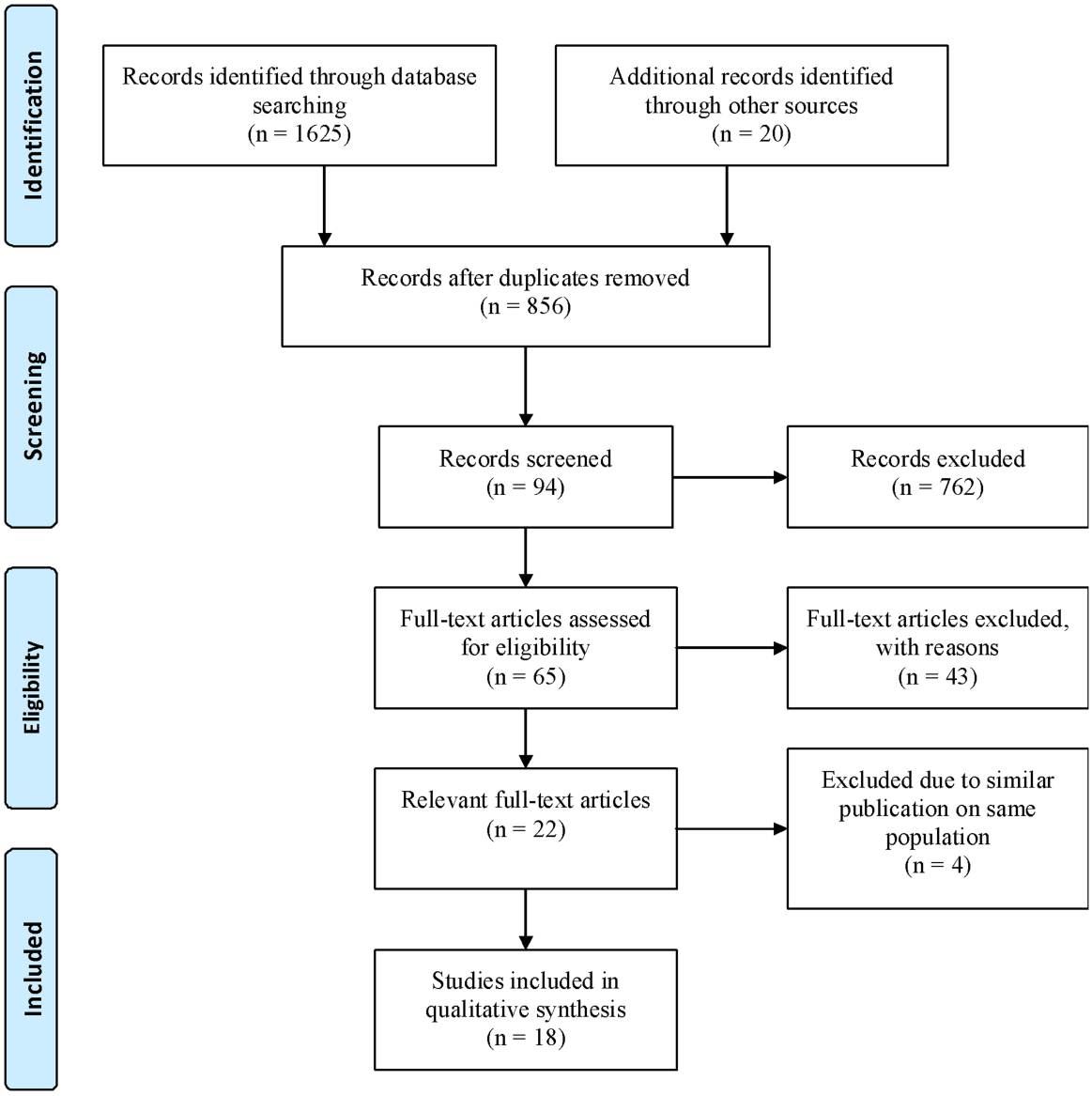

Figure 1 Overview of literature research.

is DMARD-free sustained remission (n=3). This latter outcome was defined as sustained absence of synovitis for at least 1 year after cessation of DMARD-therapy, and of all outcomes studies the closest approximation of 'cure'. Three studies had included analyses on changes in functional ability using the health assessment questionnaire (HAQ).

Radiographic joint damage in RA

Five HQ studies evaluated joint damage as outcome. Four of these (75%) demonstrated that shorter symptom duration was associated with less radiographic progression over time.[16 21 22 24] This implies that the evidence on the association between symptom duration and joint damage progression is strong. One HQ study showed the opposite, this study included a severe subset of patients with RA (>6 swollen joints, >9 tender joints, 90% anti-citrullinated protein antibody (ACPA) positivity) and compared patients with RA with symptom duration of <5 and >5 months at treatment initiation; the patients with RA who started >5 months of symptoms had a better outcome.[30] Three of the four HQ studies that reported a beneficial effect of early initiation of treatment had divided patients in groups with symptoms of <3 and >3 months, and observed that patients with symptoms <3 months at start of treatment developed less severe joint damage. Lukas *et al*[22] reported a mean SHS progression of 0.8 vs 1.7 units after 1 year, respectively (p=0.033), Nell *et al*[24] showed a mean Larson progression of 3.6 vs 14.7 after 3 years (p<0.05) and Van der Linden *et al*[21] reported a 1.3-fold higher rate of joint destruction during 6 years follow-up in patients with RA with a symptom duration of >3 months (p<0.001). In three of the six LQ studies,[12 13 27] a significant association was also observed between shorter symptom duration and less radiographic progression. Two LQ studies showed the same trend in the data, but statistical significance was not achieved (table 3).[18 25]

DMARD-free sustained remission in RA

Three HQ studies assessed DMARD-free sustained remission in patients with RA. With the permission of the authors, the raw data were used to perform a meta-analysis.[9–11] First, a meta-analyses of the univariable association between symptom

Table 2 Overview of selected papers

First author, year of publication[ref]	N	Quality score (%)	Outcome	Association between shorter symptom duration and outcome
Radiographic joint damage				
Jansen, 2001 [16]	130	79	SHS	S
Lukas, 2011 [22]	661	86	SHS	S
Nell, 2004 [24]	40	86	Larsen	S
Van der Linden, 2010 [21]	598	100	SHS	S
Weng, 2010 [30]	233	85	Sharp	NS
Bosello, 2011 [12]	121	50	Larsen or SHS	S
Dixey, 2004 [13]	866	64	Larsen	S
Kaufmann, 2003 [18]	54	43	Larsen	NS
Pascual-Ramos, 2009 [25]	72	43	Erosive (yes/no)	NS
Sanmarti, 2003 [27]	60	57	Larsen	S
DMARD-free sustained remission				
De Rooy, 2011 [10]*	676	86	DMARD-free sustained remission	S
Van der Woude, 2009 [9]* (ERAS)	895	86	DMARD-free sustained remission	S
Van der Woude, 2012 [11]* (BeSt)	508	79	DMARD-free sustained remission	NS
Other outcomes in RA				
Jayakumar, 2012 [17]†	704	85	DAS-28 <1.6‡	S
Mötönnen, 2002 [23]	199	87	ACR remission	S/NS§
Nell, 2004 [24]	40	86	DAS-28 <2.6‡ ΔHAQ	S S
Weng, 2010 [30]	233	85	DAS-44 <1.6‡ ΔHAQ score	NS NS
Bosello, 2011 [12]¶	121	47	ACR remission	S
Gremese, 2012 [14]	481	69	DAS-2.8 <2.6‡	S
Hodkinson, 2012 [15]	171	54	low SDAI	NS
Soderlin, 2011 [28]	180	69	EULAR response ΔHAQ	S S

Scored as High-quality study.
Scores as Low-quality study.
High-quality study ≥79% (which is the median of all quality scores).
*Van de Woude 2009 reported on the Leiden EAC and the ERAS; since the Leiden EAC data were represented by the De Rooy article, only the ERAS data of this article were used. Similarly, only the BeSt data were used of the van der Woude *et al* 2012 article.
†Jayakumar *et al* and van der Woude 2009 *et al* report on the same cohort however other outcomes were applied.
‡DAS remission is defined as a state, thus, an absolute DAS at a specific time point after treatment.
§Two groups were studied, in the single therapy group a significant association with symptom duration was found, by contrast with the combination therapy group.
¶This cohort is also part of the three cohorts of Gremese *et al*, but different outcomes were used, namely ACR remission and erosiveness in the Bosello *et al* article and DAS-2.8<2.6 in the Gremese *et al* article.
ACR, American College of Rheumatology; DAS, Disease activity score; EAC, early arthritis clinic; ERAS, Early Rheumatoid Arthritis Study group; Erosive (yes/no), erosive disease present or absent; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; NS, Not statistically significant Trend: almost statistically significant. RA, Rheumatoid Arthritis; S, statistically significant; SHS, Sharp–van der Heijde score.

duration and achieving DMARD-free sustained remission was performed, showing a significant beneficial effect of a shorter symptom duration (HR on DMARD-free sustained remission 0.990 (95% CI 0.984 to 0.996) per week increase in symptom duration figure 2A). Then analyses were adjusted for age, gender and applied treatment, as these variables possibly modify the effect. This revealed an almost unchanged association between symptom duration and DMARD-free sustained remission (figure 2B). Certain levels of inflammation markers or auto-antibodies are a reflection of disease severity, and are also associated with the chance of achieving DMARD-free sustained remission. Therefore, analyses were finally adjusted for age, gender, treatment, erythrocyte sedimentation rate (ESR) and presence of rheumatoid factor (RF) (anti-cyclic citrullinated peptide (CCP) was not available in all cohorts).

The adjustment factors in the latter analyses allowed differentiating between effects of patient characteristics and of symptom duration on DMARD-free sustained remission. Also, this analysis revealed that symptom duration was independently associated with DMARD-free sustained remission; each week increase in symptom duration decreased the chance of achieving DMARD-free sustained remission (HR 0.989, 95% CI 0.982 to 0.995, p<0.001, figure 2C). Assuming a linear correlation with time in the early disease stage, the HR for achieving DMARD-free sustained remission in case of 12 weeks symptom duration at treatment initiation is 0.88.

Other outcomes in RA

Eight studies reported other outcomes which were collected during DMARD-therapy. Five of these eight studies showed a significant association between shorter symptom duration and increased frequency of remission.[12 14 17 24] Of the four HQ studies, one study did not observe a significant association with symptom duration,[30] two studies found a signification association,[17 24] and one study assessed two cohorts of differently treated patients, showing a significant association in one but not in the other patient group.[23] Based on these findings, the evidence for an association between symptom duration and these remission outcomes in RA is moderate. Three of the eight studies had also assessed changes in HAQ scores. Two studies (1 HQ and

Table 3 Extended overview of selected articles

First author, year publication[ref]	Study design	Population, Location	N	Age, years *mean±SD or median (IQR)*	Female (%)	Symptom duration (months) *mean ±SD or median (IQR)*	Definition symptom onset	Outcome of relevance	Adjustment factors	Relevant results
Bosello, 2011[12]	OC	1987+ RA, Italy	121	53.6±13.3	76	5.7±3.5	NR	▶ Radiographic joint damage (defined ≥1 unit increase in of SHS/ Larsen erosions score) after 1 year FU ▶ ACR remission	▶ Sex, erosive disease, HAQ ▶ Sex, RF, ACPA, ESR, SJC	▶ *Not* having 'VERA' predictor of erosiveness at 12 months, OR 2.4 (95% CI 1.1 to 5.6) ▶ 'VERA' predictor for ACR remission , OR 5.3 (95% CI 2.1 to 13.0)
Dixey, 2004[13]	OC	1987+RA, UK (ERAS)	866	<45 : 24% 45–60: 40% >60 : 36%	66	6 (4–11)	NR	Radiographic outcome at 3 years (by Larsen score; cut-off median erosions score and the worst quartile	none	Symptom duration (weeks) on radiographic outcome, OR 1.86 (95% CI 1.30 to 2.66)
De Rooy, 2010[9]	OC	1987+ RA, Netherlands (EAC Leiden)	676	56.4±15.7	67.9	6.1±5.2	Onset of joint symptoms reported by the patient	Arthritis persistency (the reverse of DMARD-free sustained remission)	Age, sex, inclusion period (as proxy for treatment strategy)	Symptom duration (weeks) OR 1.011 on arthritis persistency (95% CI 1.002 to 1.019), p=0.012
Gremese, 2012[14]	OC (3 cohorts combined)	1987+ and 2010+ RA patients, Italy	481	54.4±12.0	74.4	6.4±3.3	NR	DAS-28 (<2.6) remission at 12 months FU	DAS-28, HAQ, ACPA, erosions, DMARDs within 3 months	'VERA' on DAS-28 remission, OR 2.03 (95% CI 1.15 to 3.30)
Hodkinson, 2012[15]	OC	1987+ RA, South-Africa	171	47.1±12.4	81.9	11.7±7.1	NR	Low disease activity (LDA) at 12 months (SDAI≤11) versus moderate/high disease activity (MDA/HDA; SDAI≥11)	None	LDA symptom duration 9.9±6.9 months vs MDA/HDA 11.7±6.8 months. (mean ±SD) Not significant (p value unknown).
Jansen, 2001[16]	OC	1987+ RA, Netherlands	130	65(21–86)	67	3 (0–24)	Onset of persistent pain and swelling reported by the patient	Δ radiographic damage at 1 year (by SHS).	None	Symptom duration was correlated with radiographic progression (p<0.005)
Jayakumar, 2012[17]	OC	1987+ RA, UK (ERAS)	704	55 (45–64)	65.6	7 (4–12)	NR	Sustained remission DAS-28<1.6 after 5 years FU	Sex, TJC, treatment and many other baseline variables	Symptom duration <6 months OR 3.15 (95% CI 1.03 to 10.0, p=0.046)
Kaufmann, 2003[18]	OC	1987+ RA, Germany	54	56 (30–38)	83.3	<6 months: 27 (50%)	NR	Radiographic progression defined by yearly increase of Larsen score ≥5.8	Age, sex, RF, HLA-DR4 SE, erosions, ESR and CRP	Symptom duration (>6 months) on severe radiographic progression OR=1.05, p value=0.826
Lukas, 2011[22]	OC	RA according to the rheumatologist, France (ESPOIR)	661	48.6±12.1	77.2	<3 months 32% >3 months 68%	Onset of swollen joints reported by the patient	Radiographic progression after 1 year of follow-up (by Δ SHS units)	DAS-28, RF, involvement>3joint groups, CRP, ACPA, treatment (propensity score)	Symptom duration <3 months vs >3 months: estimated marginal means 0.8 units (SEM 0.37) versus 1.7 units (SEM 0.19), p=0.033
Mötönnen, 2002[23]	RCT	1987+ RA, Finland (FIN-RACo)	165	Mean age varied 46–50 years between the arms	62	Combination arm: 6 (4–9) Single arm: 7 (4–11)	NR	ACR remission at 2 years FU (fatigue and duration criteria excluded)	age, sex, SE, RF and number of other ACR1987 criteria fulfilled	Estimated proportion of remission in: – The single treatment group for symptom duration 0–4 months ~36% vs >4 months ~10%, p=0.010 – The combination treatment group symptom duration 0–4 months ~43% vs >4 months ~40%, p=0.83

Continued

Table 3 Continued

First author, year publication[ref]	Study design	Population, Location	N	Age, years *mean±SD or median (IQR)*	Female (%)	Symptom duration (months) *mean ±SD or median (IQR)*	Definition symptom onset	Outcome of relevance	Adjustment factors	Relevant results
Nell, 2004[24]	OC	1987+ RA, Austria	40	54 (25–80)	75	VERA 3 (2–4) LERA 12 (9–30)	NR	▶ Radiographic progression (Δ Larsen score) ▶ DAS-28 improvement/ remission (<2.6) ▶ HAQ improvement All outcomes after 3 years FU	None	▶ VERA patients had an increase of 3.6±6.5 units compared with an increase of 14.7±9.9 Larsen units in LERA, p<0.05. (mean±SD) ▶ DAS <2.6 was obtained in 50% of VERA and 15% of the LERA patients (p<0.05). ▶ Change in HAQ score: VERA −0.7 ±0.7 (−78%), LERA −0.4±0.6 (−44%), p<0.05.
Pascual-Ramos, 2009[25]	OC	1987+ RA, Mexico	72	NR	NR	Erosive 4.9±2.9 And non-erosive dise 6.5±1.8	NR	Joint damage (erosive disease yes/no) at 1 year FU	None	Symptom duration (months) on erosive disease OR 1.16 (95% CI 0.97 to 1.4), p=0.11
Sanmarti, 2003[27]	OC	1987+ RA, Spain	60	52.2±15.7	78.3	9.5±6.5	NR	Radiographic progression at 1 year (Larsen Score; progression defined as >2 units)	All baseline variables with p<0.15 in univariable analysis	Multivariable; symptom duration n (months) OR 1.15 (95% CI 1.03 to 1.28), p<0.05
Soderlin, 2011[28]	OC	1987+ RA, Sweden (BARFOT)	180	58±15	68	5.8±12	NR	▶ 1 year good EULAR response ▶ Mean Δ HAQ change at 1 year	Age, sex, smoking, RF, HAQ, treatment, DAS-28	▶ Patients with a good/moderate EULAR response in case of symptom duration <12 weeks 81%, 13–24 weeks 82% and 25–52 weeks 76%, p=0.03. ▶ HAQ and symptom duration: correlation coefficient=0.12, p=0.0001
Van der Linden, 2010[21]	OC	1987+ RA, Netherlands (EAC Leiden)	598	56.8±15.8	67.7	4.2 (2.4–8.1)	Onset of joint symptom reported by the patient	SHS progression over 6 years based on yearly made x-rays	Age, sex, inclusion period (as proxy for treatment strategy)	Patients with symptom duration >12 weeks have a 1.34-fold higher progression ratio than patients with symptom duration <12 weeks, over a period of 6 years (p=0.001)
van der Woude, 2009[9]	OC	1987+ RA, UK (ERAS)	895	52±13	69	8.3±6	NR	DMARD-free sustained remission	All baseline variables with p<010 univariable analysis	▶ Multivariable; Symptom duration on achieving DMARD-free remission, HR 0.94 (95% CI 0.89 to 0.99), p=0.029
Van der Woude, 2012[11]	RCT	1987+ RA, Netherlands (BeSt Trial)	508	54±13.7	68	5.3 (3.2–12.2)	NR	DMARD-free sustained remission	Age, sex, DAS-44, ACPA	▶ Symptom duration on achieving DMARD-free sustained remission, OR 0.99 (95% CI 0.98 to 1.00), p=0.099

Continued

Table 3 Continued

First author, year publication[ref]	Study design	Population, Location	N	Age, years *mean±SD or median (IQR)*	Female (%)	Symptom duration (months) *mean ±SD or median (IQR)*	Definition symptom onset	Outcome of relevance	Adjustment factors	Relevant results
Weng, 2010[30]	OC	1987+ RA, USA and Mexico	233	50±13	77	5.7 (0.6–15.9)	First appearance of joint symptoms leading to diagnosis of RA	▲ Annual progression rate by total Sharp over 2 years. ▲ DAS 44<1.6 over 2 years ▲ Change in HAQ over 2 years	None	'Early' patients (<150 days symptom duration) versus 'late' patients (>150 days symptom duration at baseline) ▲ Total Sharp, units per year 3.13 ±6.49 vs 1.69±4.43, p=0.3 ▲ 2 year DAS 44<1.6: 25% vs 25%, NS (p NR) ▲ Δ HAQ −0.61±0.57 vs −0.42±0.68 NS (p NR)

ACPA, anti-citrullinated protein antibody; ACR, American College of Rheumatology; CRP, C-reactive protein; DAS, Disease activity score; EAC, early arthritis clinic; ERAS, Early Rheumatoid Arthritis Study group; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; FU, follow-up; HAQ, Health assessment questionnaire; HDA, high disease activity; LERA, late early rheumatoid arthritis; NS, Not statistically significant Trend: almost statistically significant; NR, not reported; OC, observational cohort; RCT, randomised controlled trial; RF, rheumatoid factor; SHS, Sharp-van der Heijde Score; TJC, tender joint count; VERA, very early rheumatoid arthritis.

1 LQ) reported that shorter symptom duration was associated with a higher improvement in HAQ scores.[24 28]

DISCUSSION

At present, early identification of RA and early start of DMARD therapy have become important targets in the treatment of RA. Despite the current focus on the early phases of the disease, we questioned whether very early intervention with the disease is indeed more effective with regard to modifying the disease outcome, or that positive findings are overemphasised in current thinking. We performed a systematic literature review to address this question. We identified strong evidence for an association between shorter symptom duration and less severe radiographic joint damage in patients with early RA. Furthermore a meta-analysis on the outcome DMARD-free sustained remission demonstrated that prolonged symptom duration is independently associated with a decreased chance on this remission; in case of symptom duration of 12 weeks (the suggested period of the window of opportunity) at treatment initiation the HR on remission was 0.88. At present, a DMARD-free sustained remission is the closest available proxy of 'cure' of RA; this outcome is presumably most suited to evaluate whether an early period in which the disease is most susceptible tot treatment exists. Current data supports the presence of a 'window of opportunity' effect.

This study, however, has limitations. First, this study addressed possible citation bias but not publication bias. Another major limitation is that heterogeneity in the definition of symptom onset, and consequently differences in time periods studied, prohibited us from performing a meta-analysis on all 18 selected studies. There were also large differences in study designs and study outcomes. A qualitative review was performed instead. Strengths of the current approach are that two independent readers scored all the articles, that criteria for evaluation of the quality were in line with those of previous studies,[6 7] and that predefined and stringent qualitative levels of evidence[8] were used to summarise the data (strong evidence was defined as ≥75% of the HQ studies reporting an effect in the same direction). With this approach, we tried to optimise the accuracy of this systematic qualitative literature review. An important drawback of a systematic literature review is that by simply counting the number of positive and negative studies, the sample sizes and power of the individual studies was ignored. Hence, studies with a tendency in the data that were underpowered to obtain a significant result were considered equally negative as studies with true negative findings. With a qualitative systematic literature review, the data can also not be presented in a funnel plot because an overall effect size cannot be generated.

The fact that a systematic literature review and meta-analysis may result in a slightly different answer is illustrated here with the data on achieving DMARD-free sustained mission. Three HQ studies were found. Two studies[9 10] were significant; the third[11] was not significant but showed a tendency towards an effect of symptom duration on remission (HR 0.99 (95% CI 0.98 to 1.00), p=0.099 in multivariable analysis). Given the predefined levels of evidence (table 1), two out of three positive studies would result in the conclusion that there is a moderate level of evidence for an association between symptom duration and DMARD-free sustained remission. However, in the meta-analyses there was a consistent and independent association between symptom duration and DMARD-free sustained remission.

Another difficulty when interpreting the results of the present study is the fact that different studies had included different

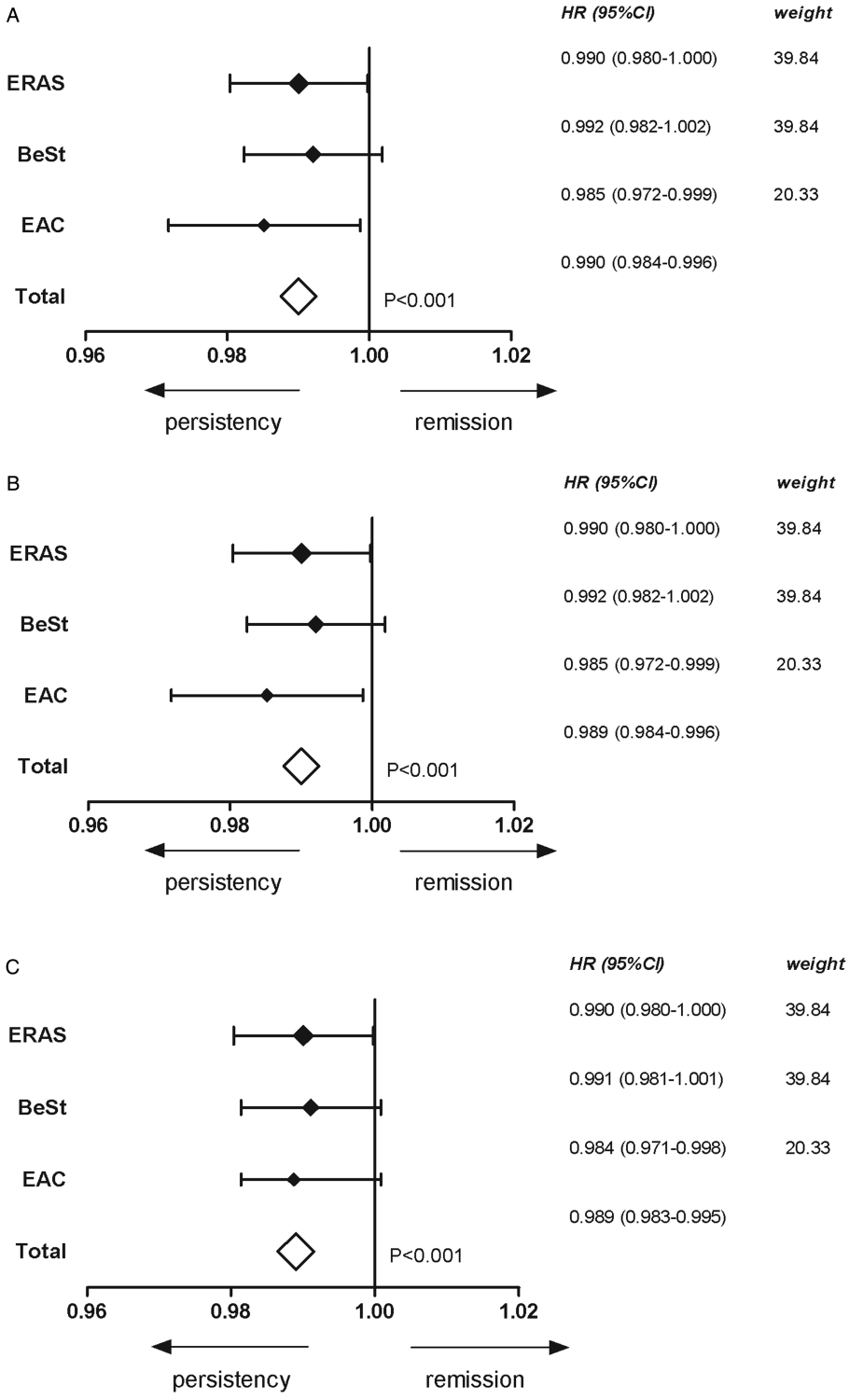

Figure 2 Meta-analysis on the association between symptom duration (in weeks) and achieving DMARD-free sustained remission over time in rheumatoid arthritis (RA). (A) Univariable analysis on symptom duration, heterogeneity p=0.72, I^2=0.0. (B) Multivariable analysis on symptom duration, adjusted for age, gender and treatment, heterogeneity p=0.72, I^2=0.0. (C) Multivariable analysis on symptom duration, adjusted for age, gender, treatment, rheumatoid factor and ESR, heterogeneity p=0.70, I^2=0.0. The follow-up durations studied were similar as in the articles, 10 years for Early Rheumatoid Arthritis Study group (ERAS), 5 years for BeSt and 10 years for the Leiden early arthritis clinic. The number of patients with RA included in these three datasets with complete data for current analysis were n=892, n=507 and n=505, respectively. De Rooy; in the original article: the term persistency was used; in the meta-analysis we used the reverse, namely 'DMARD-free sustained remission' A decreased chance on achieving a DMARD-free sustained remission is equal to an increased chance on arthritis persistency.

adjustment factors in the analyses (see table 3). Not adjusting for patient and disease characteristics and treatment effects may potentially result in findings that are not driven by symptom duration but by the association of these factors with disease outcome. In 12 of the total 18 studies, 11 of the 14 positive studies, and seven of the 10 HQ-studies adjustments for patient and disease characteristics were applied, though not exactly the same factors. Four of the 10 HQ studies applied adjustments for differences in treatment. Furthermore, Mottönen *et al*[23] observed a significant association in the single therapy group but not in the combination therapy group. In the meta-analyses on DMARD-free sustained remission, the association between symptom duration and disease outcome was independent of patient characteristics (age, gender), disease characteristics (ESR as marker of inflammation and RF as marker of autoantibody positivity) and the applied treatment strategies. The drugs used in the studies that applied adjustments for treatment were conventional DMARDs[10 17 21 23 28] and/or biologics.[14 22]

Some studies evaluated symptom duration and had divided patients in groups of, for example, symptoms for >5 and

<5 months,[17 18 30] meaning that patients in both groups had passed the period of the 'window of opportunity' that was previously defined as the first 12 weeks.

Our formulated inclusion and exclusion criteria resulted in a selection of studied articles. A large proportion of screened articles was not included in this review because of not fulfilling the inclusion criteria. Some studies investigated patients with early (poly)arthritis, but not specifically RA, and were, therefore, not included.[31 32] Several of the excluded studies did show that patients with RA with shorter symptom duration had a better outcome. For example, Green *et al*[33] reported on disease persistency after 6 months in inflammatory patients with polyarthritis treated with corticosteroids, and observed that patients with symptom duration <12 weeks more often achieved remission. This study had 6 months of follow-up and did not fulfil our inclusion criteria of ≥1 year of follow-up. The latter was also the case for the study of Saevarsdottir *et al*[34] on the SWEFOT trial, observing that prolonged symptom duration was associated with a lower chance on achieving a good EULAR response after 3–4 months methotrexate treatment. Several papers were excluded because the period between diagnosis and treatment onset was studied but not the period between symptom duration and treatment onset,[35–39] or because the patients studied had symptoms >2 years.[40–42] We acknowledge that the maximum of 2 years symptom duration as definition of early RA is arbitrary, though given our study question, we decided to focus on early RA.

In conclusion, the present systematic literature review observed that in early patients with RA who were mostly treated with conventional DMARDs, there is strong evidence that prolonged symptom duration is associated with severe joint damage progression. Additionally, a meta-analysis on achieving DMARD-free sustained remission observed an independent association for symptom duration. These results, therefore, support the notion of the presence of a 'window of opportunity'. The details of the time frame (evaluation of when the window 'opens' and 'closes') are left to be explored in the near future. Many studies using uniform definitions of symptom onset are required to this end; definitions for standardised durations were recently proposed.[5]

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Supplemental file 2. Methodological quality assessment form and search criteria per database.

OC: observation cohort study. RCT: randomized-controlled trial studies:

Paper: **Reader:**		
Item	**Criteria**	Applicable for:
1	**<u>Definition of study population</u>** **Sufficient description of characteristics of study groups** *A '1' is given when a paper describes at least setting and time period of the study, ages of patients (and its range) and man:woman ratio*	OC /RCT
2	**<u>Definition of diagnosis</u>** **RA diagnosis was according to the 1987 ACR or 2010 ACR/EULAR classification criteria .**	OC /RCT
3	**<u>Selection bias</u>** **Clear description of selection of study subjects.** *When a paper described how the study subjects were selected (description of in- and exclusion criteria) from the population level to the study level, a '1' will be given.*	OC/ RCT
4	**<u>Follow-up</u>** **Follow up time ≥ 2 years for RA patients.** *More than 2 years was seen as an acceptable follow up duration to assess RA outcome (such as sustained DMARD-free or radiographic progression).*	OC/ RCT
5	**Organization of follow-up** *A '1' was given if there was a structured follow-up applied. So not only on patients request.*	OC/ RCT
6	**Participation rate ≥ 80% for study groups** *80% was an arbitrary margin chosen to determine the quality of the selection of study subjects.*	RCT
7	**No differences in lost to follow-up (in both groups)**. *Including (quantative and qualitative) information on completers and non-completers*	OC/RCT
8	**<u>Assessment of symptom duration</u>** *Symptom onset is clearly defined as symptoms such as pain or*	OC/ RCT

	swelling reported by the patient or swelling observed by the physician/rheumatologist.	
9	**<u>Assessment of the outcome: valid measures of disease activity , joint-damage or remission</u>** *For disease activity; DAS-28, DAS 44 or SDAI. For (radiologic) joint-damage measures; SHS, LARSON score or RAMRIS. For Remission; DMARD-free remission defined by the rheumatologist and the DMARD-free remission period should be given*	OC/ RCT
10	**Radiologic outcome assessment was blinded to clinical data (at least treatment and symptom duration)** *A '1'is given if the observers were blinded to the intervention and symptom duration when for example scoring the radiographs.*	OC/ RCT
11	**Outcome measure was assessed reproducibly** *For example A '1'is given if an ICC/Kappa is provided concerning radiographic outcomes. Or if internal or external validation is provided in relation to prediction rules. In case of remission; if DMARD-free period is given or if (DAS)remission was still present in the follow-up visit at the rheumatologist.*	OC/ RCT
	<u>Analysis and Data Presentation</u>	
12	**Frequencies of symptom duration was given**	OC/ RCT
13	**Frequencies of important outcomes studied were given**	OC/ RCT
14	**Appropriate analysis techniques with estimates were used**	OC/ /RCT
15	**Adjusted for at least age and gender and treatment strategy/arm.**	OC/ RCT
	TOTAL QUALITY RATE	**With radiographic outcome;** **OC …/14** **RCT …/15** **Without radiographic outcome;** **OC …/13** **RCT …/14**

Overview of the search per database.

Total d.d. 11-5-2012: 836 references, extracted from the following databases:

- MEDLINE (OVID): 452
- PubMed: 164, of which 14 unique
- Embase: 606 (of which 164 meeting abstracts): 297 unique
- Web of Science: 278, of which 54 unique
- COCHRANE: 18, of which 1 unique
- CINAHL: 46, of which 13 unique
- Academic Search Premier: 51, of which 5 unique
- ScienceDirect: 10, of which 0 unique

PubMed

(rheumatoid arthritis OR "rheumatoid arthritis" OR "Arthritis, Rheumatoid"[Mesh:noexp] OR rheumatoid OR arthritis[tiab] OR arthritic) AND ("symptom duration" OR "complaint duration" OR ((symptom*[ti] OR complaint*[ti]) AND duration*[ti]) OR ((symptom*[ti] OR complaint*[ti]) AND "Time Factors"[mesh]))

MEDLINE (OVID-version)

(rheumatoid arthritis.mp OR "rheumatoid arthritis".mp OR Arthritis, Rheumatoid/ OR rheumatoid.mp OR arthritis.ti,ab OR arthritic.mp) AND ("symptom duration".mp OR "complaint duration".mp OR ((symptom*.ti OR complaint*.ti) AND duration*.ti) OR ((symptom*.ti OR complaint*.ti) AND exp Time Factors/) OR (symptom* **ADJ6** duration*).mp OR (complaint* **ADJ6** duration*).mp)

Embase (OVID-version)

(rheumatoid arthritis.mp OR "rheumatoid arthritis".mp OR rheumatoid arthritis/ OR rheumatoid.mp OR arthritis.ti,ab OR arthritic.mp) AND ("symptom duration".mp OR "complaint duration".mp OR ((symptom*.ti OR complaint*.ti) AND duration*.ti) OR (symptom* **ADJ6** duration*).mp OR (complaint* **ADJ6** duration*).mp)

Web of Science

(TS=(rheumatoid arthritis OR "rheumatoid arthritis" OR rheumatoid) OR TI=arthriti*) AND (TS=("symptom duration" OR "complaint duration") OR TI=((symptom* OR complaint*) AND duration*) OR TS=((symptom* **NEAR/5** duration*) OR (complaint* **NEAR/5** duration*)))

Cochrane Library

(rheumatoid arthritis OR "rheumatoid arthritis" OR rheumatoid OR arthriti*) AND ("symptom duration" OR "complaint duration" OR "duration of symptoms" OR "duration of symptom" OR "duration of complaints" OR "duration of complaint")

CINAHL

(rheumatoid arthritis OR "rheumatoid arthritis" OR rheumatoid OR arthriti*) AND ("symptom duration" OR "complaint duration" OR "duration of symptoms" OR "duration of symptom" OR "duration of complaints" OR "duration of complaint")

Academic Search Premier

(rheumatoid arthritis OR "rheumatoid arthritis" OR rheumatoid OR arthriti*) AND ("symptom duration" OR "complaint duration" OR "duration of symptoms" OR "duration of symptom" OR "duration of complaints" OR "duration of complaint")

A. ScienceDirect

TITLE-ABSTR-KEY((rheumatoid arthritis OR "rheumatoid arthritis" OR rheumatoid OR arthriti*) AND ("symptom duration" OR "complaint duration" OR "duration of symptoms" OR "duration of symptom" OR "duration of complaints" OR "duration of complaint"))

Supplementary table 1. Results of the study quality assessment scores in alphabetical order of first Author. (1: present, 0: absent or no information) Scores solved by discussion are in italics.

Author, year (Ref)	Criteria															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total score
Bosello, 2011(12)	0	1	0	0	1	N/A	0	0	1	0	1	1	1	1	0	7/14=50%
Dixey, 2004 (13)	***1***	1	1	1	1	N/A	0	0	1	0	0	1	1	1	0	9/14=64%
De Rooy, 2010 (9)	1	1	1	1	1	N/A	***0***	1	1	1	1	1	***1***	1	***0***	12/14=86%
Gremese, 2012 (14)	1	1	1	0	1	N/A	0	0	1	N/A	0	1	1	1	1	9/13=69%
Hodkinson, 2012 (15)	1	1	0	0	1	N/A	0	0	1	N/A	0	1	1	1	0	7/13=54%
Jansen, 2001 (16)	1	1	1	0	1	N/A	***1***	***1***	1	1	0	1	1	1	0	11/14=79%
Jayakumar, 2012 (17)	1	1	1	1	1	N/A	0	0	1	N/A	1	1	1	1	***1***	11/13=85%
Kaufmann, 2003 (18)	0	1	0	1	0	N/A	0	0	1	1	0	***0***	1	1	0	6/14=43%
Lukas, 2011 (22)	1	1	1	***0***	1	N/A	1	***1***	1	1	1	0	1	1	1	12/14=86%
Mötönnen, 2002 (23)	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	13/15=87%
Nell, 2004 (24)	1	1	1	1	1	N/A	1	0	1	1	1	1	1	1	0	12/14=86%
Pascual-Ramos, 2009 (25)	0	1	1	0	1	N/A	0	0	***0***	0	0	1	1	1	0	6/14=43%
Sanmarti, 2003 (27)	1	1	0	***0***	1	N/A	0	0	1	0	***1***	1	***1***	1	0	8/14=57%
Soderlin, 2011 (28)	1	1	1	0	1	N/A	***0***	0	1	N/A	0	1	1	1	1	9/13=69%
Van der Linden, 2010 (21)	1	1	1	1	1	N/A	1	1	1	1	1	1	1	1	1	14/14=100%
van der Woude, 2009 (9)	1	1	1	1	1	N/A	1	0	1	1	1	1	1	1	0	12/14=86%
Van der Woude, 2012 (11)	1	1	1	1	1	1	0	0	1	N/A	1	1	1	1	***0***	11/14=79%
Weng, 2010(30)	1	1	1	0	1	N/A	0	***1***	1	1	1	1	1	1	0	12/14=86%