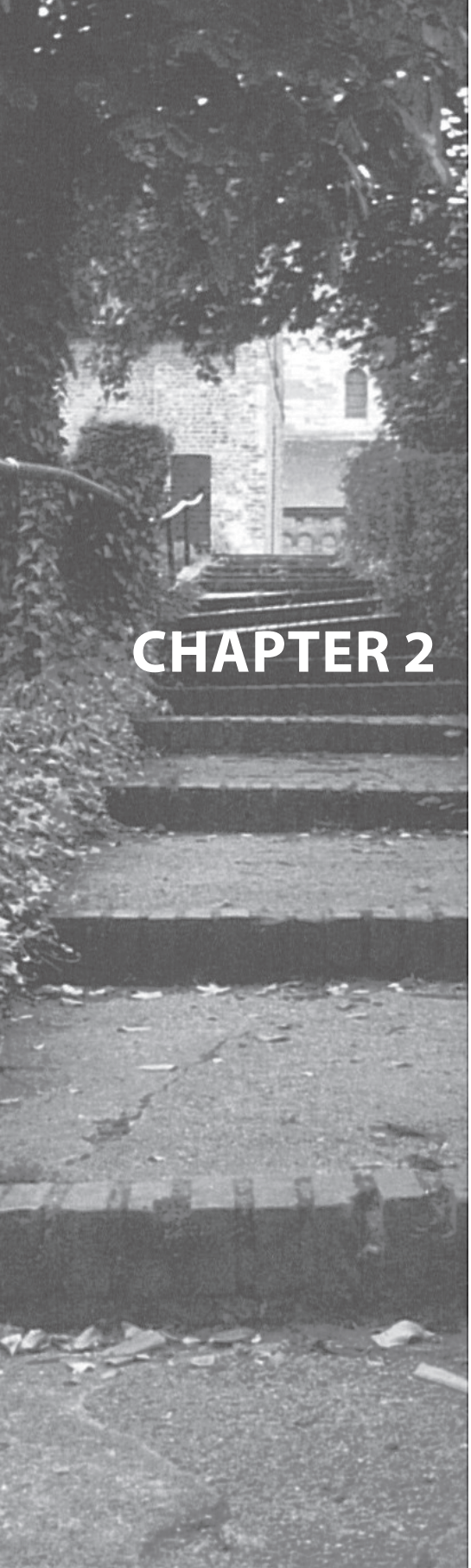

CHAPTER 2

Drug therapy in undifferentiated arthritis: a systematic literature review

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ABSTRACT

Objective

Undifferentiated arthritis (UA) is defined as an inflammatory oligo- or polyarthritis in which no definitive diagnosis can be made. We performed a systematic literature review to assess the efficacy of various drug therapies in patients with UA.

Methods

The systematic literature search was conducted using electronic databases Pubmed, EMBASE and MEDLINE in adults with undifferentiated or early arthritis (not fulfilling the ACR 1987 or ACR/EULAR 2010 criteria for RA). Drug therapy consisted of disease modifying anti-rheumatic drugs (DMARDs), biological agents and oral, intra-muscular (IM) or intra-articular corticosteroids.

Results

Nine publications on 8 randomized controlled trials (RCTs), 2 publications on 2 uncontrolled open-label trials and 7 publications on 3 cohort studies were included. Temporary treatment with methotrexate (MTX), abatacept and IM corticosteroids were demonstrated in RCTs with 12 months to 5 years follow up to be more effective than placebo in suppressing disease activity or radiologic progression. One study suggests that DMARD combination therapy is, at least after 4 months, superior to MTX monotherapy in UA patients at high risk of developing persistent arthritis. The open label uncontrolled trials and cohort studies also suggested that early treatment may provide immediate suppression of inflammation. The long term benefit of early treatment in UA remains unclear.

Conclusions

UA patients benefit from early treatment with MTX. Combining multiple DMARDs or DMARDs with corticosteroids and biological agents may be even more beneficial. However, which treatment may provide the best results or may alter the disease course still has to be determined. More randomized clinical trials with longer follow up time are needed.

INTRODUCTION

Undifferentiated arthritis (UA) is defined as an inflammatory oligo- or polyarthritis in which no definitive diagnosis can be made, and which over time may naturally evolve into a chronic inflammatory disease or into remission. Several observational cohorts of early arthritis patients have shown that, depending on the inclusion criteria, 17-32% of the patients progress to rheumatoid arthritis (RA),[1] while 40-55% achieve spontaneous remission.[2,3]

Since many studies have proven that early treatment of RA improves clinical, functional and radiological outcomes,[4-6] the question has risen if treatment in the stage of UA may be even more beneficial. The so called 'window of opportunity theory' hypothesizes that in an early stage of RA, possibly in the stage of UA, a period may exist in which the disease course can be altered by the appropriate treatment, preventing it from becoming a chronic and disabling disease.[7] In 2010, new classification criteria have been published to enable earlier diagnosis and treatment of RA patients.[8] Recent data have shown that patient indeed are diagnosed earlier,[9] but the benefit of the new criteria in terms of long term disease outcome still needs to be elucidated. Furthermore, also with these new criteria part of the patients with inflammatory oligo- or polyarthritis cannot (yet) be classified as RA.

To investigate whether early initiation of disease modifying anti-rheumatic drugs (DMARDs) is beneficial for patients with UA, we performed a systematic literature review to identify all articles on disease outcomes of drug treatment in patients with UA, and aimed to assess the efficacy of the different drug therapies.

METHODS

The systematic literature search was conducted using electronic databases Pubmed, EMBASE and MEDLINE and restricted to adults with UA or early arthritis (not fulfilling the ACR 1987 or ACR/EULAR 2010 classification criteria for RA). The following definitions were searched for up to February 2012: undifferentiated or early or unclassified or probable (inflammatory) arthritis or oligo- or polyarthritis. Drug treatment was restricted to glucocorticosteroids, DMARDs and biological agents. Articles were only included if they concerned disease outcomes of drug therapy. All types of publications were included and no language restrictions were used.

Using predefined inclusion criteria, titles and abstracts were screened by one researcher and checked up by a second researcher. Disagreements were solved by discussion. Of the selected articles, full texts were screened for final selection in the review. Reference lists of included review articles were hand searched for additional relevant articles. Data extraction was performed by one researcher. Methodological quality of included randomized controlled trials (RCTs) was assessed by two independent researchers following the Guidelines for Cochrane Musculoskeletal Group Systematic Reviews, using the Cochrane Collaboration's

tool for assessing risk of bias.[10] For each study, the risk of several types of bias (selection, performance, detection, attrition and reporting bias and 'other sources of bias') was judged and summarized in an overall risk as low, high or unclear. Also, the Jadad score was performed, a quality score assessing randomization, blinding, withdrawals and drop outs.[11] Scores range from 0-5 with higher scores indicating better methodological quality.

Because of the large heterogeneity in types of patients, drug therapies and outcome measures no meta-analysis was performed.

RESULTS

After screening 3608 titles and abstracts, 67 articles were screened full text.

In total 30 articles were selected: 11 on 10 clinical trials of which 8 were RCTs and 5 placebo controlled, 7 on 3 cohort studies, and 10 review/opinion articles and 2 recommendations which were disregarded for this analysis.(figure 1)

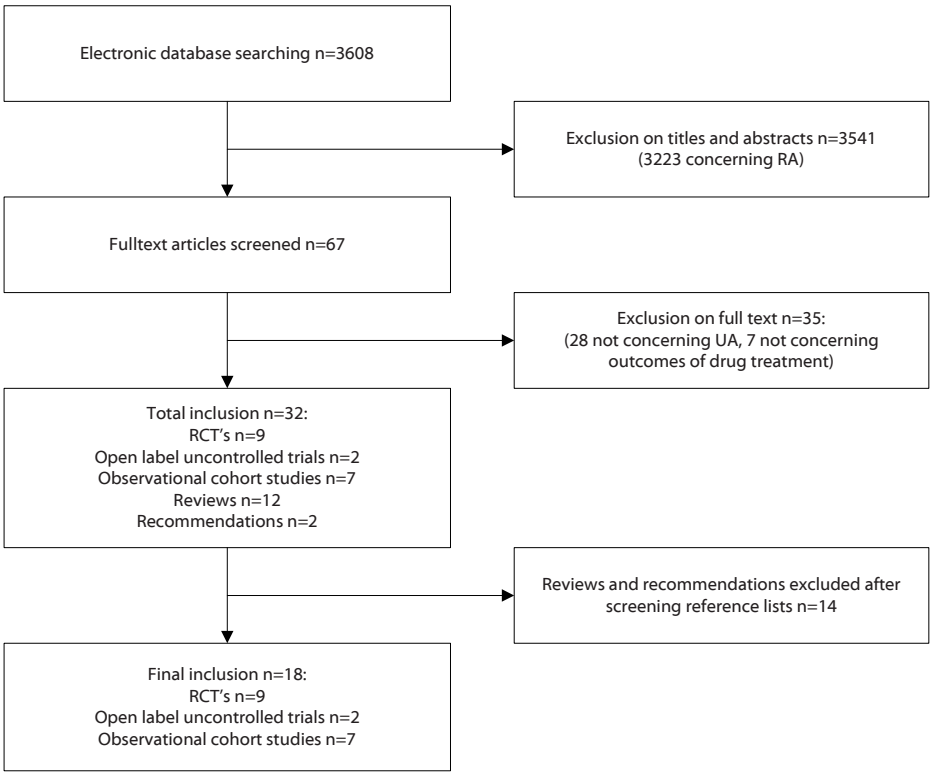

Figure 1: Flow diagram of systematic literature search for publications on drug treatment of patients with undifferentiated arthritis.

Characteristics of clinical trials are shown in table 1. Three trials included both UA and RA patients.[12-14] Drug therapies studied were intra-muscular (IM) or intra-articular (IA) corticosteroids (3 RCTs, 2 placebo controlled, 1 open label trial), DMARDs with or without oral glucocorticoids (GCs) (2 RCTs, 1 placebo controlled, 1 open label trial), biological agents (2 placebo controlled RCTs) and one RCT comparing tight control with 'routine DMARD' treatment. On one placebo controlled RCT two articles with different follow up duration were published.

Characteristics of observational studies are shown in table 2. Five of 7 publications were based on the Norfolk Arthritis Register (NOAR), a primary care-based cohort in adults with ≥2 swollen joints for at least 4 weeks, of which 46% at baseline fulfilled the 1987 criteria for RA.[15] Four studies compared treated and untreated patients and/or early versus delayed start of treatment. Adjustments for differences in disease severity or time dependent confounders between groups were made using propensity scores or marginal structural models (MSM). One publication comparing anti-citrullinated protein antibodies (ACPA) positive and negative patients and two publications without comparisons between treated and/or untreated patients are not further mentioned.

Main outcomes of all included clinical trials are shown in table 3. Seven clinical trials investigated temporary treatment and 3 trials continuous tight controlled treatment. Follow up varied between 3 months and 5 years. Many different outcome measures were used for assessing response to treatment in terms of disease activity state, achieving remission, joint damage or progression to RA.

Results of synthetic DMARDs

Van Dongen et al [16] and van Aken et al [17] compared a 12 months course of methotrexate (MTX) with placebo after 30 months and 5 years follow up. After 30 months 22 (40%) in the MTX group and 29 (53%) in the placebo group had progressed to RA(1987 criteria) (p value not published), after 5 years 25 (45%) and 29 (53%) did (p=0.45). Remission was achieved in comparable numbers after 30 months and 5 years (after 30 months 15 (27%) and 13 (24%) and after 5 years 20 (36%) and 15 (27%) in the MTX and placebo group respectively (p-values not published)). All patients in the placebo group who progressed to RA did so within one year compared to half of the patients in the MTX group (p=0.04), suggesting that progression to RA was at least postponed by one year of MTX treatment. After 30 months, more patients showed radiological progression in the placebo group (14 versus 6, p=0.046), but after 5 years median SHS progression did not differ between groups (p=0.78). Up to 30 months, fewer adverse events (AE) were reported in the placebo group, serious AE (SAE) were reported similarly in both groups.

De Jong et al [14] compared MTX monotherapy with MTX+sulphasalazine (SSZ)+hydroxychloroquine (HCQ) in early arthritis patients at high risk for developing persistent arthritis according to the prediction model of Visser et al.[18] All patients received GC bridging therapy (either a tapering scheme or IM injection). After three months, the combination therapy group

Table 1: Characteristics of clinical trials on drug treatment in patients with early or undifferentiated arthritis.

Study	Year	Type	N	FU	Inclusion criteria	Used definition	Intervention	Primary outcome	Bias risk	Jadad score
Corticosteroid injections										
Green [21]	2001	Open label	51	1 yr	Synovitis ≤5 joints, ≤12 months	'Early oligoarthritis'	Methylprednisolone IA (all arthritic joints)	No clinical synovitis	-	-
Marzo-Ortega [22]	2007	RCT	59	1 yr	Synovitis ≤4 joints, <12 months	'Early oligoarthritis'	Methylprednisolone IA (all arthritic joints) vs NSAIDs, SSZ in case of polyarthritis	Absence of synovitis	High	3
Machold [23]	2010	RCT	389	1 yr	Arthritis ≥1 joints, <16 weeks	'Very early arthritis'	Methylprednisolone IM vs placebo, 1 injection	Clinical remission*	Mod	3
Verstappen [24]	2010	RCT	268	1 yr	Arthritis ≥2 joints, 4-10 weeks	'Early polyarthritis'	Methylprednisone IM vs placebo, 3 injections	Need to start DMARD after 6 months	Low	5
DMARDs										
Van Dongen [16]	2007	RCT	110	30 mo	Probable RA (1958 ACR criteria)	'Probable RA'	MTX vs placebo	Progression to RA, radiological progression	Mod	2
Van Aken [17]	2013	RCT	110	5 yrs	Probable RA (1958 ACR criteria)	'Probable RA'	MTX vs placebo	Progression to RA, radiological progression	Mod	2
De Jong [14]	2012	RCT	281	3 mo	Arthritis ≥2 joints, < 1 year, high likelihood of persistent arthritis	'Early arthritis' (88% RA(2010))	MTX+oralGC vs MTX+SSZ+HCQ +oralGC vs MTX+SSZ+HCQ + IM GC	DAS, HAQ	High	3
Wevers-de Boer [13]	2012	Open label	122	4 mo	≥1 arthritic and ≥1 painful joints, suspect for RA	'Early arthritis' (79% RA(2010))	MTX + tapered high dose prednisone	Remission (DAS<1.6)	-	-
Tight control strategy										
Van Eijk [12]	2012	RCT	82	2 yrs	2-5 swollen joints, <2 years	'Early arthritis' (69% RA(2010))	Remission targeted treatment** vs conventional care	Radiological progression	High	2
Biologicals										
Saleem [19]	2008	RCT	17	6 mo	Arthritis >1 joint, <12 months	'UA'	Infliximab vs placebo	Clinical remission	Mod	2
Emery [20]	2010	RCT	56	18 mo	Arthritis ≤3 criteria of 1987 ACR criteria for RA	'UA'	Abatacept vs placebo	Progression to RA	Mod	4

* clinical remission defined as no swollen joints, <2 tender joints, no treatment other than study drug, 2 of 3 criteria: a) normal C-reactive protein (CRP), b) visual analogue scale (VAS) disease activity <1, c) VAS pain <1

**start with MTX 15 mg, in case of no remission: subsequently switch to MTX + adalimumab, increase adalimumab, switch to MTX+SSZ+HCQ, add prednisone.

DAS, disease activity score; DMARD, disease modifying anti-rheumatic drugs; FU, follow up; GC, Glucocorticosteroids; HAQ, health assesment questionaire; HCQ, hydroxychloroquine; IA, intra-articular; IM, intra-muscular; Jadad score, quality assessment score ranging from 0-5 with higher scores indicating better methodological quality; Mod, moderate; MTX, Methotrexate; N, number of patients; NSAID, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis according to the American College of Rheumatology (ACR) 1987 classification criteria; RA(2010), RA according to the ACR/European League Against Rheumatism (EULAR) 2010 classification criteria; RCT, randomized controlled trial; Risk of bias, assessed according to the Cochrane Collaboration's tool for assessing risk of bias; SSZ, Sulfasalazine, UA, undifferentiated arthritis.

Table 2: Characteristics of observational cohort studies in patients with early inflammatory polyarthritis.

Study	Year	N	FU	Inclusion criteria	RA *	ACPA+ *	RF+ *	Comparison	Outcomes	Adj. for severity bias
Wiles [27]	2001	384	5	Swelling ≥2 joints, ≥4 weeks	49%	np	31%	Treatment vs no treatment, early vs delayed treatment	Functional ability	PS
Bukhari [26]	2003	335	5	Swelling ≥2 joints, ≥4 weeks	47%	np	31%	No vs early treatment vs delayed treatment	Radiologic progression	PS
Farragher [15]	2010	642	10	Swelling ≥2 joints, ≥4 weeks	np	np	np	Treatment vs no treatment, early vs delayed treatment	Functional ability	MSM
Lukas [25]	2011	661	1	Arthritis >2 joints, 6 weeks - 6 months, high suspicion for RA	73%	41%	45%	Early vs delayed treatment	Radiologic progression	PS

*at baseline

Three of 7 selected articles on observational cohort studies were not mentioned in this table because no comparisons between early versus delayed treatment were made.

ACPA, anti-citrullinated protein antibodies; Adj, adjustments; DMARD, disease modifying anti-rheumatic drugs; FU, follow up in years; MTX, methotrexate; MSM, marginal structural model; N, number of patients; np, not published; PS, propensity scoring; RA, rheumatoid arthritis according to the 1987 ACR classification criteria; RF, rheumatoid factor; vs, versus.

Table 3: Main outcomes of clinical trials included in the systematic review

Study	Symptom duration (wks)	ACPA+ (%)	RF+ (%)	Female (%)	Age (yrs)	Baseline disease activity		Disease activity response /state		Remission (%)		Joint damage		Progression to RA (%)	Time to prog. to RA
Temporary treatment						**Definition**		**Definition**		**Definition**		**Definition**			
Green [21]	16	NR	22	55	42	*Arthritic joints (median)*	2.3	*No synovitis 12 wks (%)*	45	*ACR1981 52 wks*	18		NR	NR	NR
Marzo-Ortega [22]															
CS IA (1-3 times)	12	NR	6	42	34	*SJC (no.)*	1	*No synovitis 52 wks (%)*	81		NR		NR	NR	NR
Conservative care	10		4	43	31		1		57						
Machold [23]															
CS IM (once)	9	NR	NR	72	48	*Oligo-arthritis (%)*	41	*Persistent remission* 52 wks (%)*	16	*Remission* 12 wks*	22		NR	45	NR
Placebo	8			76	48		36		18		21			51	
Verstappen [24]															
CS IM (3 times)	8	NR	31	68	56	*Mean DAS28(3)*	5.3±1.2	*DAS28(3) 26 wks (mean)*	3.7	*'resolved disease' 52 wks*	**20** #	*Development of erosions 52 wks (%)*	13	49	NR
Placebo	8		35	69	55		5.3±1.2		3.7		**10**		15	60	
Van Dongen [16]															
MTX (12 mo)	45	22	36	64	51	*Mean DAS*	2.7	*Remission 30 mo*	>	*DAS<1.6 30 mo*	27	*SHS progression 30 mo (%)*	**11 †**	40	**HR 1.7‡**
Placebo	38	27	35	69	51		2.5				24		**25**	53	
Van Aken [17]															
MTX (12 mo)	45	22	36	64	51	*Mean DAS*	2.7	*Remission 5 yrs*	>	*DFR DAS<1.6 5 yrs*		*SHS progression 5 yrs (median)*	0 (0-1)	45	**100¶**
Placebo	38	27	35	69	51		2.5						0 (0-1)	53	**44**
Saleem [19] **															
Infliximab (14 wks)	32	8/10	7/10	8/10	51	*Mean DAS28*	5.3	*Remission 26 wks*	>	*No synovitis CRP<10 26 wks*	2/10		NR	10/10	26 wks
Placebo	36	4/7	3/7	6/10	58		4.3				1/7			5/7	14 wks
Emery [20]															
Abatacept (6 mo)	35	NR	86	71	45	*Mean DAS28 (CRP)*	3.6	*Remission 52 wks*	>	*DAS28(CRP) <2.6 52 wks*	47	*Difference in G-mS TS 52 wks*	**-1.1††**	46	NR
Placebo	28		71	71	45		3.4				39		ref	67	

Table 3: Main outcomes of clinical trials included in the systematic review (Continued)

Study	Symptom duration (wks)	ACPA+ (%)	RF+ (%)	Female (%)	Age (yrs)	Baseline disease activity		Disease activity response /state		Remission (%)		Joint damage		Progression to RA (%)	Time to prog. to RA
Continuous treatment						**Definition**		**Definition**		**Definition**		**Definition**			
Van Eijk [12]															
Tight Control	24	60	48	58	48	*Mean DAS*	2.2±0.5	*Mean DAS*	1.4	*DAS*	66	*Median*	0	NR	NR
Conventional care	24	60	33	79	46		2.4±0.7	*2 yrs*	1.7	*<1.6*	49	*increase SHS*	0.25		
										2 yrs		*2 yrs*			
De Jong [14]															
MTX	22	58	53	70	54	*Mean DAS*	3.4±1.0	*Difference in*	ref	*DAS<1.6*	31		NR	NR	NR
Mutiple DMARDS	25	59	58	66	54		3.3±1.0	*mean DAS*	**-0.4 ‡‡**	*3 mo*	44				
								3mo							
Wevers-de Boer [13]															
RA	18	68	69	70	52	*Mean DAS*	3.3±0.9	*Mean DAS*	1.5	*DAS<1.6*	61	*Median SHS*	0	NR	NR
UA	16	3	4	61	52		2.7±0.7	*4 mo*	1.4	*4 mo*	65	*progression*	0		
												4 mo			

* clinical remission defined as no swollen joints, <2 tender joints, no treatment other than study drug, 2 of 3 criteria: a) normal CRP, b) VAS disease activity<1, c) VAS pain<1

** because of small number of study participants, for this study no./total was presented instead of percentages.

Significant differences are pressed bold

OR 0.42 (0.18-0.99), p=0.048

† p=0.046

‡ p=0.04

†† 95% CI (-2.1; -0.2)

‡‡ 95% CI (-0.7; -0.1)

¶ % progression to RA within 1 year; Kaplan Meier Survival analysis after 5 years: MTX versus placebo p=0.11, ACPA positive patients versus ACPA negative patients: p<0.001

ACPA, anti-citrullinated protein antibodies; ACR1981: preliminary criteria for clinical remission in RA, ACR 1981; CRP, C-reactive protein; CS, corticosteroids; DAS, original disease activity score; DAS28, disease activity score based on 28 joint count; DAS28(3), DAS28 3 components; DFR, drug free remission; G-mS TS, Genant modified Sharp total score; IA, intra-articular; IM, intra-muscular; mo, months; NR, not reported; RF, rheumatoid factor; ref, reference; SJC, swollen joint count; wks, weeks; yrs, years.

had a lower mean Disease Activity Score (DAS) than the monotherapy group (difference (95% CI) 0.39 (0.67-0.11)). No significant difference was seen between oral and IM GC bridging therapy. AE and SAE were reported in 67 (75%) and 50 (56%) in the combination therapy and the monotherapy group. Fewer medication changes were made in the monotherapy group (14 (16%) versus 18 (20%), p=0.006).

In an open label trial in patients with UA or recent onset RA(2010 criteria),[13] MTX was combined with a tapered high dose of prednisone for 4 months. Remission after 4 months was achieved in 79 (65%) UA and 291 (61%) RA patients (p=0.5). Median (IQR) SHS progression was 0 (0-0) in both UA and RA patients (p=0.9). AE were reported in 341 (56%) and SAE in 16 (3%) of all patients.

These studies indicate that synthetic DMARDs suppress disease activity in UA patients. MTX monotherapy may postpone but not prevent the development of RA and may slow down radiological progression. It appears that initial combination therapy with MTX and multiple DMARDs or corticosteroids (oral or parenteral) results in better short term clinical outcomes. No long term data are available.

Results of biological DMARDs

Two trials have investigated biological agents in UA patients. Saleem et al [19] compared a 14 week course of infliximab with placebo in UA patients who had relapsed after a single corticosteroid injection. If clinical inflammation was persistent after week 14, MTX was started. Independent safety monitors halted recruitment 'because of poor outcomes in all subjects' before inclusion was completed, after inclusion of 17 patients (10 randomized to infliximab, 7 to placebo) Clinical remission at 26 weeks was achieved in 1 patient and 2 patients in the placebo and infliximab group respectively. After 1 year, all patients in the infliximab group had progressed to RA (1987 criteria) compared to 5/7 in the placebo group, in which this occurred earlier (after a median of 14 compared with 26 weeks, respectively). Data on (S)AE were not reported.

Emery et al [20] compared a six months course of abatacept with placebo. After 1 year, respectively 12 (46%) and 16 (67%) of the abatacept and placebo group progressed to RA(1987 criteria) (difference (95% CI) -21% (-47% to 8%)). Radiologic progression (Genant-modified Sharp score) after one year was significantly less in the abatacept group (difference in total score -1.10 (95% CI -2.05 to -0.15)). Remission (DAS28 definition) after 1 year was achieved in 9 (47%) and 5 (39%) in the abatacept and placebo group respectively. Numbers of reported AE and SAE were similar.

These trials suggest that a biological agent may slow down progression to RA in UA patients. Early treatment with abatacept appears to suppress radiological damage progression. Long term benefits remain uncertain.

Results of corticosteroid injections

Green at al [21] performed an open label pilot with IA GC injections in all arthritic joints in 51 patients. Clinical synovitis was absent in 23 (45%) and 26 (51%) after 12 weeks one year respectively.

Marzo-Ortega et al [22] injected all inflamed joints with GC (early intervention (EI) group) and compared this with 'conservative treatment' (CT group) with a nonsteroidal anti-inflammatory drugs (NSAID). In case of progression to polyarthritis SSZ was started. Clinical synovitis was absent in 25 (81%) and 16 (57%) patients after 52 weeks in the EI and CT group respectively (p=0.05), but more patients in the EI group started DMARD treatment (14 (45%) versus 4 (14%), p=0.012). The EI group reported a significantly lower mean Visual Analogue Scale (VAS) pain after 4 weeks than the CT group, but not after 12 and 52 weeks. Data on (serious) AE were not reported.

Machold et al [23] compared a single IM injection of GC with placebo. Respectively 32 (16%) and 33 (18%) in the GC and placebo group achieved persistent remission without additional treatment after 1 year (p=0.68). Initiation of a DMARD and core set variables were comparable. AE generally were mild and comparable between groups.

Verstappen et al [24] compared a three week course of IM GC injections with placebo. When patients met ≥2 of 4 predefined criteria (≥3 swollen joints, ≥6 painful joints, morning stiffness ≥45 minutes or erythrocyte sedimentation rate ≥28 mm/h), they were referred for DMARD treatment. After 6 months, patients in the placebo group were more often referred for DMARD treatment than the GC group (96 (76%) versus 77 (61%), adjusted OR (95% CI) 2.11 (1.16-3.85), p=0.015). After 1 year, remission without DMARD use was less often achieved in the placebo group (11 (10%) versus 22 (20%), adjusted OR (95% CI) 0.42 (0.18-0.99), p=0.048). Sixty seven (60%) and 54 (49%) in the placebo and GC group were classified as RA(1987 criteria) (adjusted OR (95% CI) 1.58 (0.85-2.93), p=0.15). AE were comparable between groups.

These studies indicate that a single corticosteroid injection probably has no long term benefit. Repeated IM corticosteroid injections may postpone the need to start DMARDs but not prevent progression to RA, and in one study possibly encourage remission. No long term follow up data exist.

Results of tight control and treat to target strategies

Van Eijk et al [12] compared tight control treatment (TC group) with conventional care (CC group) in early arthritis patients. The TC group (n=42) started with MTX monotherapy, medication was intensified in case of no remission (19 patients changed to adalimumab, 15 increased adalimumab, 11 switched to multiple DMARDs , 3 added prednisone and 1 switched to leflunomide). The CC group (n=40) used conventional DMARDs without treatment target (24, 14 and two patients started HCQ, MTX and SSZ respectively). No prednisone or biologics were allowed. After 2 years, respectively 66% and 49% in the TC and CC group were in remission (numbers and p-value not published). Median SHS progression was 0 (0-1.0) and 0.25 (0-2.5)

in the TC and CC group (p=0.17). Over two years, no significant differences in DAS and Health Assessment Questionnaire (HAQ) levels were seen. The number of reported AE was higher in the TC group (62 versus 35, p=0.03). The number of SAE was comparable.

In conclusion, this trial shows no benefit to patients with UA of tight control treatment over conventional care in terms of radiological and clinical outcomes and achieving remission.

Early versus delayed treatment

No RCTs compared early versus delayed start of treatment in patients with UA. In an open label study [13] no difference in proportions remission was found between UA and RA (2010 criteria) patients after a four months of MTX and a tapered high dose of prednisone. But although UA patients had a lower baseline DAS, baseline symptom duration was similar between UA and RA patients.

In an observational study in the ESPOIR cohort, Lukas et al [25] compared early versus delayed treatment, adjusted for selection bias using propensity scores. The estimated marginal mean (SE) SHS progression was 0.8 (0.37) and 1.7 (0.19) in patients who respectively started DMARD therapy within and after 3 months (p=0.03). Stratification in propensity quintiles showed that only patients with high baseline disease activity starting DMARD therapy after 3 months showed more progression than patients starting within 3 months.

Bukhari et al [26] found a similar result in the NOAR cohort, also using propensity scores. Starting treatment within 6 months after symptom onset was associated with less radiologic damage after 5 years than starting after 6-12 months and >12 months (OR (95% CI) 1.5 (0.9-2.3) versus 2.3 (1.4-3.9) and 2.2 (1.4-3.5) respectively, with untreated patients as reference (1.0)).

Wiles et al [27] compared early versus delayed treatment in the NOAR cohort using propensity scores, with functional ability after 5 years as outcome. Starting treatment early (within 6 months of symptom onset) was not associated with a HAQ score ≥1.0 (OR 0.71 (0.34 to 1.44), but starting treatment after 6-12 and >12 months was (OR (95% CI) 1.98 (0.86 to 4.54) and 2.03 (1.10-3.75) respectively, with untreated patients as reference (1.0)). Farragher et al [15] used functional ability after 10 years as outcome and adjusted for time dependent confounders using MSM. Patients treated within 6 months after symptom onset improved more in functional ability than untreated patients, although not significantly (difference (95% CI) in change from baseline HAQ -0.24 (-0.58-0.09)). In patients treated after 6-12 months and >12 months functional ability improved less than in untreated patients (difference (95% CI) in change from baseline of respectively 0.12 (-0.13;0.37) and 0.18 (-0.06;0.41)). For each month that treatment was started earlier within 6 months, a significant additional benefit was found (difference (95% CI) in change from baseline HAQ -0.10 (-0.19 to -0.02) per month).

In conclusion, results from these observational cohort studies may indicate that disease outcomes improve if treatment is started within at the most six months after symptom onset, and starting sooner may even be better.

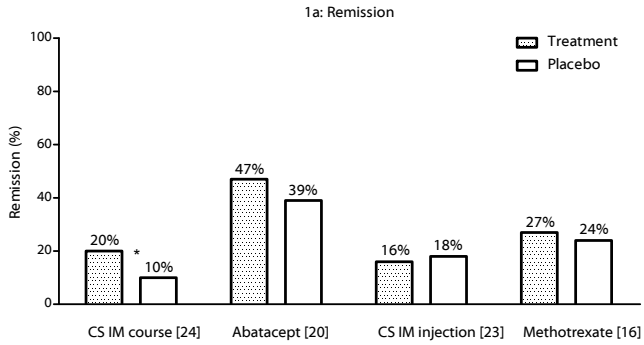

Figure 2a: Remission percentages after one year [24,20,23] and 30 months [16] follow up of the four completed placebo controlled trials on temporary treatment of patients with undifferentiated arthritis * significant difference.

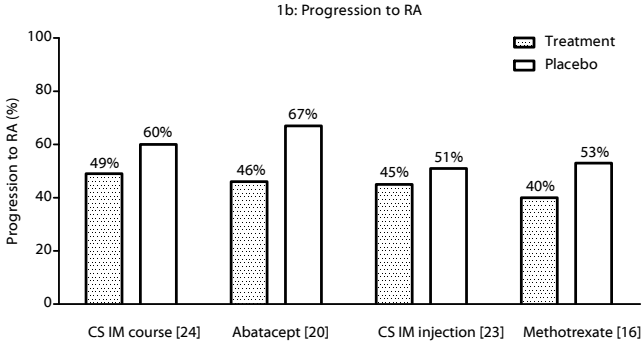

Figure 2b: Percentages of patients who progressed to rheumatoid arthritis after one year [24,20,23] and 30 months [16] follow up of the four completed placebo controlled trials on temporary treatment of patients with undifferentiated arthritis.

DISCUSSION

This systematic literature review shows that to date, few placebo controlled RCTs have been done to answer the question if early treatment in patients with undifferentiated arthritis is beneficial and which treatment might be the best. To compare results is difficult because of inconsistent outcome measures. Five clinical trials, two open label studies and four observational studies suggest that starting treatment early may provide symptom relief, improve functional ability and suppress radiological progression. It may also postpone progression to classifiable RA or the need for other therapies. The strongest evidence of a potential benefit is present on early treatment with MTX, possibly in combination with other DMARDs or corti-

costeroids. Observational studies, which by using propensity scoring and minimal structural models try to partially compensate for indication bias, suggest that other DMARDs than MTX may be used. Data from these cohorts also suggest that starting treatment in UA may be a case of 'the earlier the better'. The benefit of earlier treatment has been previously demonstrated for patients with RA.[4,5,28,29] But contrary to what is recognized and recommended for patients with classifiable RA,[30,31] one study suggests that patients with UA may not gain additional benefit from tight controlled targeted treatment.[12]

The ultimate goals in the treatment of UA would be to prevent progression to destructive RA or even induce permanent remission. Achieving these goals would mean that the so called 'window of opportunity', in which appropriate treatment can alter the disease course, does exist. The closest evidence for the presence of the window of opportunity possibly comes from a study in 253 UA patients,[24] where after a three week course of IM corticosteroid injections more patients achieved remission (20% versus 10%), fewer required initiation of DMARDs (61% versus 76%) and possibly fewer progressed to classifiable RA than in the placebo group (49% versus 60%). Also 6 months abatacept appears to suppress progression to RA, at least over 1 year follow up, although no statistically significant difference was found possibly due to small numbers.[20] Similarly, a one year course of MTX suppressed progression to RA and radiological progression, but after discontinuation of MTX the disease appeared to rerun its course.[16,17] None of the articles included data on sustained drug free remission.

Over diagnosing as 'early RA' followed by overtreatment is a serious concern when treating patients with UA, or even patients who according to the new 2010 criteria would now be classified as RA. Patients may have another illness that may go into spontaneous remission. The solution may lay in predicting disease outcome, such as persistent arthritis or radiologic progression, or response to treatment. Prediction models for disease outcome have been developed.[18,32] However, to predict disease outcome and response to treatment in individual patients is not yet possible.

In conclusion, there are limited trials and observational studies exploring the possibility of inducing remission and/or permanently altering the disease course in UA patients. Long term follow up data are mostly not available. During treatment with MTX monotherapy, combination therapy with multiple DMARDs or corticosteroids, biological agents and intra-muscular corticosteroid injections, active inflammation and ensuing radiographic damage may be suppressed. Early initiation of treatment may be better than delayed initiation, in particular if disease activity appears to be high. Thus, we should optimize strategies for early referral and early identification of patients with arthritis. In addition, any new randomized clinical trials in UA patients should include a short term placebo arm to investigate if early treatment can induce (drug free) remission and a long term follow up period to demonstrate if early treatment can alter the disease course.

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