

**SUPPLEMENTARY MATERIAL**

**Supplementary Table S1**.....

**Supplementary Table S2**.....

**Supplementary Table S3**.....

**Supplementary Table S4**.....

**Research questions** .....

**Flowcharts**.....

**Research strategies** .....

**Supplementary Table S1. Face-to-face efficacy comparisons of csDMARD monotherapy with intensive therapy: i) csDMARD combination therapy; ii) tsDMARD; iii) bDMARD.**

Study [level of evidence]	Study type	Population	Drug regimens	Primary outcome(s)	Clinical evaluation	Radiographic evaluation
<b>Nam J Ann Rheum Dis 2014 IDEA study [1b](1)</b>	DB RCT then OLE	112 treatment-naive early RA patients	<u>Blinded up to w26:</u> 1) MTX + IFX 2) MTX + PBO + single dose IV-MP 250 mg T2T: if DAS44 >2.4, IM-MP 120 mg or IA-GC.	Change in mTSS at w50	<b>w26-DAS44 remission:</b> IFX 40% vs IV-MP 31.6% (adjusted OR 0.82 [0.36 to 1.88]; p=0.644).	<b>w26 changes in mTSS:</b> IM-MP: 1.52 (4.25); IFX: 0.83 (1.69); p=0.29
<b>Nam J Ann Rheum Dis 2014 EMPIRE [1b](2)</b>	RCT then OLE	110 patients with early clinical synovitis and either RF/ACPA/SE	<u>Blinded up to w52:</u> 1) MTX+ETN 2) MTX +PBO. No GC use (only 1 IM or IA permitted)	No tender or swollen joints (NTSJ) at week 52.	<b>NTSJ at week 52:</b> ETN 32.5% vs PBO 28.1% (adjusted OR 1.32 [0.56 to 3.09], p=0.522)	NA
<b>Detert; Ann Rheum Dis 2013 HIT HARD [1b](3)</b>	DB superiority RCT	172 DMARD-naïve early RA	<u>2 arms for 24w:</u> 1) ADA+MTX 2) PBO+MTX	DAS28 at w48	<b>w24 DAS28:</b> ADA+MTX: 3.0±1.2; PBO+MTX: 3.6±1.4 (p=0.009) <b>W24 DAS28 remission:</b> ADA+MTX: 47.9%; PBO+MTX: 29.5% (p=0.021)	NA
<b>Atsumi Ann Rheum Dis 2015 C-OPERA [1b](4)</b>	DB superiority RCT.	316 MTX-naive, early <b>high risk RA</b> patients	<b>1) CZP+MTX</b> <b>2) PBO+MTX</b> <u>If DAS28-ESR≥3.2 for ≥4 w after w24: open label CZP</u>	Change in mTSS at w52	<b>SDAI remission w24:</b> CZP+MTX: 48.4% ; PBO+MTX: 29.3% ; p<0.001.	<b>Change in mTSS at w24:</b> CZP+MTX: 0.26 (1.55); PBO+MTX: 0.86 (2.37); p=0.003
<b>Takeuchi Ann Rheum Dis 2014 HOPEFUL-1 [1b](5)</b>	DB superiority RCT	344 patients with <b>high risk RA</b> with ≥1 joint erosion or RF+	<u>2 arms for 26w:</u> ADA+ MTX 6–8 mg/w PBO+MTX 6–8 mg/w <u>Rescue: if &gt;20% increase from baseline in TJC or SJC at w12, 16 or 20: open-label</u>	Δ mTSS w26-w0	<b>ACR 20 response w26:</b> ADA+MTX 75.4% vs PBO+MTX 56.5%, p<0.001; Idem for ACR50/70 and remission criteria (p<0.001).	<b>ΔmTSS w26-w0:</b> ADA+MTX: 1.5±6.1 ; PBO+MTX: 2.4±3.2 (p<0.001) <b>ΔmTSS≤0.5 w26-w0:</b> ADA+MTX: 62% vs PBO+MTX: 35.4% ; (p<0.001)

			ADA			
<b>Emery, EULAR 2015 abstract SAT0164, C-EARLY [1b](6)</b>	DB RCT	DMARD-naïve early active RA	1) CZP+MTX 2) PBO+MTX MTX at 10mg/w increased to 25mg/w	Sustained remission (SR): DAS28 ≤2.6 at W40 and W52	<b>SR w52:</b> CZP+MTX: 28.9%; PBO+MTX: 15.0%; OR=2.3; p<0.001	<b>ΔmTSS w52:</b> CZP+MTX: 0.2; PBO+MTX: 1.9 (p<0.001)
<b>Burmester Ann Rheum Dis 2015 FUNCTION [1b](7)</b>	DB RCT	1162 early RA patients	4 arms: 4 mg/kg TCZ +MTX ; 8 mg/kg TCZ +MTX ; 8 mg/kg TCZ +PBO ; PBO+MTX	DAS28 remission at w24	<b>W24 DAS28-remission:</b> 4 mg TCZ+MTX:92 (31.9%) ; 8 mg TCZ+MTX: 130 (44.8%) ; 8 mg TCZ+PBO: 113 (38.7) ; PBO+MTX: 43 (15.0%)	<b>mean Δ mTSS w52:</b> 4 mg TCZ+MTX 0.42 (2.93); 8 mg TCZ+MTX 0.08 (2.09); 8 mg TCZ+PBO 0.26 (1.88); PBO+MTX 1.14 (4.30) 8 mg TCZ+MTX vs PBO+MTX: p=0.0001
<b>Bijlsma; EULAR 2015 OP0033 U-ACT-EARLY STRATEGY STUDY [1b](8)</b>	DB RCT	317 patients with early RA and no previous DMARD	<u>3 arms:</u> initial regimen -TCZ (8 mg/kg IV /4 w) -MTX (10 mg increased at 30 mg/w until remission or dose-limiting toxicity) -TCZ+MTX HCQ could be added. <u>Treat-to-target strategy</u>	Sustained remission (SR) rate during the 2-year study (DAS28<2.6 SJC≤4 for ≥23 w, with the exception of ≤2 visits).	<b>SR rates during initial regimen:</b> TCZ: 84% ; MTX: 44% ; TCZ+MTX: 86% (p<0.001 for TCZ+MTX vs MTX and TCZ vs MTX; p=0.62 for TCZ+MTX vs TCZ),	<b>NA</b>
<b>Emery P. Ann Rheum Dis 2015 AVERT [1b](9)</b>	DB superiority RCT	351 ACPA+ early RA patients (<4w of MTX)	<u>12-month treatment and then stop:</u> <b>1) ABA (SC 125 mg) + MTX;</b> <b>2) MTX</b> <b>3) ABA</b>	% of patients with DAS28-CRP <2.6 at 12 Mo and at both 12 and 18 Mo, for ABA+MTX vs MTX.	<b>DAS28-CRP &lt;2.6 at 12 Mo:</b> ABA + MTX: 60.9% ; MTX: 45.2% (ABA+MTX vs MTX: p=0.010); ABA: 42.5%	

\* High-risk early RA patients: (erosions + RF+ and/or ACPA+) OR (erosions + DAS28-CRP>3.2) OR (RF+ and/or ACPA+ and DAS28-CRP>3.2); \*\* RA patients with bad prognosis: ≥3 erosions or IgM-RF+ or ACPA+. mTSS: modified total Sharp-van der Heijde score; OLE: open label extension

**Supplementary Table S2. Comparison of safety between intensive (csDMARD combination, tsDMARD and bDMARD respectively) and less intensive therapy in patients with early arthritis.**

Study	Drug regimens	Patients with ≥1 or number of AE related to therapy	Infection	Serious AE	Withdrawal for safety reason or death
Verschueren; Ann Rheum Dis 2015 CareRA (10)	<p><b>COBRA Classic:</b> MTX+ SLZ+60 mg/d GC tapered to 7.5 mg from W7 (n=98)</p> <p><b>COBRA Slim:</b> MTX+30 mg/d GC tapered to 5 mg from W6 (n=98)</p> <p><b>COBRA Avant-Garde:</b> MTX+ LEF +30 mg GC tapered to 5 mg from W6 (n=94)</p>	<p><b>Number of AE</b> (% of patients with AE):</p> <p><b>Classic:</b> 148 (61.2%)</p> <p><b>Slim:</b> 70 (46.9%)</p> <p><b>Avant-garde:</b> 130 (69.1%)</p> <p><b>p=0.006</b></p>	<p><b>Classic:</b> 3 (3%)</p> <p><b>Slim:</b> 3 (3%)</p> <p><b>Avant-garde:</b> 5 (5%)</p>	<p><b>Classic:</b> 2 (2%)</p> <p><b>Slim:</b> 1 (1%)</p> <p><b>Avant-garde:</b> 3 (3.2%)</p>	<p><b>Classic:</b> 2 (2%)</p> <p><b>Slim:</b> 1 (1%)</p> <p><b>Avant-garde:</b> 1 (1%)</p>
tREACH: De Jong ; Ann Rheum Dis 2014 (11)	<p>3 arms:</p> <p><b>initial tritherapy iTDT (MTX + SSZ + HCQ) with IM-GCs;</b></p> <p><b>iTDT with oral GC tapering scheme</b></p> <p><b>MTX with oral GCs (iMT)</b></p>	<p><b>Patients with ≥1 AE:</b></p> <p><b>iTDT-IM:</b> 76 (84%)</p> <p><b>iTDT-oral:</b> 82 (88%)</p> <p><b>iMT:</b> 77 (79%)</p>	<p><b>iTDT-IM:</b> 12 (13%)</p> <p><b>iTDT-oral:</b> 21 (23%)</p> <p><b>iMT:</b> 22 (23%)</p>	<p><b>iTDT-IM:</b> 5 (5%)</p> <p><b>iTDT-oral:</b> 10 (11%)</p> <p><b>iMT:</b> 10 (10%)</p>	<p><b>iTDT-IM:</b> 1 (1%)</p> <p><b>iTDT-oral:</b> 0</p> <p><b>iMT:</b> 2 (2%)</p> <p><u>Medication adjustment due to AE:</u></p> <p><b>iTDT:</b> 60/93 (65%) vs <b>iMT:</b> 44/97 (45%) p=0.008</p>
Kuijper; ACR 2014 abstract 2815.[1b]	T2T aiming for a DAS<2.4 with similar intensification steps for the 3 arms in order: (1) MTX+ETN, (2) MTX+ADA, (3) MTX+ABA-IV	NA	NA	NA	NA
COBRA-light study: Den Uyl; Ann Rheum Dis 2014 (12)	<p><b>COBRA:</b> GC at 60 mg/d, tapered to 7.5 mg/d in w6 + MTX 7.5 mg/w + SSZ 2 g/d</p> <p><b>COBRA-light:</b> GC at 30 mg/d, tapered to 7.5 mg/d in w9 + MTX (escalated to 25 mg/w)</p> <p><b>T2T:</b> if DAS44≥1.6 at <b>w13</b>, MTX dose increased or SC; at <b>w26</b>, TNFi introduction.</p>	<p><b>Patients with ≥1 AE:</b></p> <p><b>COBRA:</b> 94%</p> <p><b>COBRA-light:</b> 90%</p>	<p><b>COBRA:</b> 6%</p> <p><b>COBRA-light:</b> 5%</p>	<p><b>COBRA:</b> 3 (3.7%)</p> <p><b>COBRA-light:</b> 6 (7.4%)</p>	<p><b>COBRA:</b> 1 (1.2%)</p> <p><b>COBRA-light:</b> 1 (1.2%)</p>
Ter Wee; Ann Rheum Dis 2015 [1b](13)		<p><b>Patients with ≥1 AE:</b></p> <p><b>COBRA:</b> 96%</p> <p><b>COBRA-light:</b> 96%</p>	<p><b>COBRA:</b> 3 (4%)</p> <p><b>COBRA-light:</b> 9 (11%)</p>	<p><b>COBRA:</b> 9 (11%)</p> <p><b>COBRA-light:</b> 16 (19.8%)</p>	<p><b>COBRA:</b> 3 (3.7%)</p> <p><b>COBRA-light:</b> 1 (1.2%)</p>
OPERA : Axelsen Ann Rheum Dis 2015 (14) & Hørslev-Petersen Ann Rheum Dis	<p><u>2 arms:</u></p> <p><b>MTX+IA-GC+PBO</b></p> <p><b>MTX+IA-GC+ADA</b></p> <p><b>+ triamcinolone hexacetonide in swollen joints</b></p>	NA	<p><u>Serious infection:</u></p> <p><b>ADA:</b> 3 (3.7%)</p> <p><b>PBO:</b> 3 (3.7%)</p>	<p><b>ADA:</b> 4 (5%)</p> <p><b>PBO:</b> 11 (14%)</p>	<p><b>ADA:</b> 2 (2.5%)</p> <p><b>PBO:</b> 1 (1%)</p>

**2014 OPERA**

[1b](15)

<b>Nam J Ann Rheum Dis 2014 IDEA study [1b] (1)</b>	<u>Blinded up to w26:</u> MTX + IFX or MTX + PBO + single dose IV-MP 250 mg	<b>IFX:</b> 98.2% (54/55) <b>PBO+IV-MP:</b> 94.7% (54/57)	<u>Pulmonary/upper respiratory:</u> <b>IFX:</b> 11.3% (42/369) <b>PBO+IV-MP:</b> 13.8% (51/372) <u>Serious infection:</u> <b>IFX:</b> 2(3.6%) <b>PBO+IV-MP:</b> 2 (3.5%)	<b>IFX:</b> 20 (25.3 for 100 p.y) <b>PBO+IV-MP:</b> 9 (11 for 100 p.y)	<b>IFX:</b> 2 (3.6%) <b>PBO+IV-MP:</b> 1 (1.7%)
<b>Nam J Ann Rheum Dis 2014 EMPIRE [1b](2)</b>	<u>Blinded up to w52:</u> MTX+ETN or MTX +PBO	<b>ETN</b> =451.6 events per 100 p.y <b>PBO</b> =417.3 per 100 p.y	<u>Infections:</u> <b>ETN:</b> 90 in 43 patients <b>PBO:</b> 105 in 37 patients	<b>ETN:</b> 16.4 per 100 p.y <b>PBO:</b> 3.7 per 100 p.y (but only 1 case of SAE related to ETN)	<b>ETN:</b> 2 (3.6%)/2 (3.6%) (w52/w78) <b>PBO:</b> 0/0 (w52/w78)
<b>Detert; Ann Rheum Dis 2013 HIT HARD [1b](3)</b>	<u>2 arms for 24w:</u> ADA+MTX PBO+MTX <u>After w24:</u> ADA and PBO stopped. All patients continued MTX mono. GC≤10 mg/d permitted	<b>NA</b>	<u>Serious infection:</u> <b>ADA+MTX:</b> 3 (3.4%) <b>PBO+MTX:</b> 4 (4.7%)	<b>ADA+MTX:</b> 12 (13.7%) <b>PBO+MTX:</b> 22 (19.5%)	<u>w0-w24:</u> <b>ADA+MTX:</b> 2 (2.3%) <b>PBO+MTX:</b> 4 (4.7%) <u>After w24:</u> <b>ADA+MTX-&gt;MTX:</b> 2 (2.4%) <b>PBO+MTX:</b> 3 (4.1%)
<b>Burmester Ann Rheum Dis 2015 FUNCTION [1b](7)</b>	4 arms: <b>8 mg/kg TCZ+MTX</b> <b>8 mg/kg TCZ+PBO</b> <b>4 mg/kg TCZ+MTX</b> <b>PBO+MTX</b>	<b>8 mg/kg TCZ+MTX:</b> 256 (88.3%) <b>8 mg/kg TCZ+PBO:</b> 138 (47.3%) <b>4 mg/kg TCZ+MTX:</b> 256 (88.6%) <b>PBO+MTX:</b> 235 (83.3%)	<b>8 mg/kg TCZ+MTX:</b> 137 (47.2%) <b>8 mg/kg TCZ+PBO:</b> 138 (47.3%) <b>4 mg/kg TCZ+MTX:</b> 155 (53.6%) <b>PBO+MTX:</b> 136 (48.2%)	<b>8 mg/kg TCZ+MTX:</b> 31 (10.7%) <b>8 mg/kg TCZ+PBO:</b> 25 (8.6%) <b>4 mg/kg TCZ+MTX:</b> 29 (10%) <b>PBO+MTX:</b> 24 (8.5%)	<b>8 mg/kg TCZ+MTX:</b> 10/7 % (w24/52) <b>8 mg/kg TCZ+PBO:</b> 5/6 % (w24/52) <b>4 mg/kg TCZ+MTX:</b> 6/4 % (w24/52) <b>PBO+MTX:</b> 4/2 % (w24/52)
<b>C-OPERA [1b] Atsumi Ann Rheum Dis 2015(4) ACR 2015 (16)</b>	2 arms: <b>CZP+MTX</b> <b>PBO+MTX</b> If DAS28-ESR≥3.2 for ≥4 w after w24: open label CZP	<b>CZP:</b> 153 (96.2%) <b>PBO:</b> 148 (94.3%)	<b>CZP:</b> 97 (61.0%) <b>PBO:</b> 87 (55.4%)	<b>CZP:</b> 13 (8.2%) <b>PBO:</b> 14 (8.9%)	<b>CZP:</b> 9 (5.7%) <b>PBO:</b> 6 (3.8%)

<b>TOMERA Durez P. EULAR 2013 [2b](17)</b>	<b>2 arms:</b> TCZ vs MTX <b>At w24:</b> MTX mono up-to 20 mg/w for everyone			<b>TCZ:</b> 1 (5/9%) (diverticulitis) <b>MTX:</b> 0	
<b>OPTIMA [1b] Smolen Lancet 2014(18)</b>	<u>Up to w26:</u> ADA+MTX (initiated at 7.5 mg/week, increased up to 20 mg/w at w8) PBO+MTX <u>After w26:</u> if DAS28<3.2 and ADA+MTX group, randomization ADA continuation or ADA withdrawal. If DAS28<3.2 and PBO+MTX, MTX continuation	<u>period 2</u> <b>ADA contin (LDAS+ no LDAS):</b> 75 (71.4%)/19 (76.8%) <b>ADA withdr:</b> 79 (77.5%) <b>MTX contin:</b> 83 (74.1%) <b>ADA start:</b> 270 (77.6%)	Serious infections <u>period 2</u> <b>ADA contin (LDAS+ no LDAS):</b> 6/4 (5.7/1.5%) <b>ADA withdr:</b> 4 (3.9%) <b>MTX contin:</b> 2 (1.8%) <b>ADA start:</b> 8 (2.3%)	<u>period 2</u> <b>ADA contin (LDAS+ no LDAS):</b> 12 (11.4%)/18 (6.9%) <b>ADA withdr:</b> 11 (10.8%) <b>MTX contin:</b> 9 (8%) <b>ADA start:</b> 32 (9.2%)	<u>period 1</u> <b>ADA:</b> 19/515 (3.7%) <b>PBO:</b> 15/517 (2.9%) <u>period 2</u> <b>ADA contin (LDAS+ no LDAS):</b> 3+14 / 105+259 (2.9/5.4%) <b>ADA withdr:</b> 7/102 (6.9%) <b>MTX contin:</b> 6/112 (5.4%) <b>ADA start:</b> 20/348 (5.7%)
<b>Takeuchi Ann Rheum Dis 2014 HOPEFUL-1(5) [1b]</b>	ADA+ MTX 6–8 mg/w PBO+MTX 6–8 mg/w	<b>ADA:</b> 138 (80.7%) <b>PBO:</b> 117 (71.8%) Site reaction: <b>ADA:</b> 18 (10.5%) <b>PBO:</b> 6 (3.7%), p=0.02	<b>ADA:</b> 59 (34.5%) <b>PBO:</b> 48 (29.4%)	<b>ADA:</b> 1 (0.6%) <b>PBO:</b> 1 (0.6%)	<u>Before rescue:</u> <b>ADA:</b> 7 (4.1%) <b>PBO:</b> 4 (2.5%) <u>After rescue:</u> <b>ADA:</b> 0 <b>PBO:</b> 1 (0.6%)
<b>Emery P. Ann Rheum Dis 2015 AVERT(9) [1b]</b>	<b>3 arms:</b> ABA (SC 125 mg)+ MTX vs MTX vs ABA <b>At Mo 12:</b> Patients with DAS28-CRP<3.2 entered withdrawal period; ABA stopped immediately and MTX and steroids tapered over 1 month. Patients with DAS28-CRP≥3.2 discontinued the study.	<u>Patients with ≥1 AE:</u> <b>ABA+MTX:</b> 101 (84.9%) <b>ABA:</b> 93 (80.2%) <b>MTX:</b> 96 (82.8%)	<u>Serious infection:</u> <b>ABA+MTX:</b> 1 (0.8%) <b>ABA:</b> 4 (3.4%) <b>MTX:</b> 0	<b>ABA+MTX:</b> 8 (6.7%) <b>ABA:</b> 14 (12.1%) <b>MTX:</b> 9 (7.8%)	<b>ABA+MTX:</b> 2 (1.7%) <b>ABA:</b> 5 (4.3%) <b>MTX:</b> 3 (2.6%)
<b>Emery, EULAR 2015 abstract SAT0164, C-EARLY(6)</b>	<u>2 arms for 52w:</u> CZP+MTX PBO+MTX MTX at 10mg/w and increased to 25mg/wk GC use not described	<b>NA</b>	<u>Infection:</u> <b>CZP+MTX:</b> 71.8/100 PY <b>PBO+MTX:</b> 52.7/100 PY <u>Serious infection:</u> <b>CZP+MTX:</b> 3.3/100 PY <b>PBO+MTX:</b> 3.7/100 PY	<b>NA</b>	<u>Deaths:</u> <b>CZP+MTX:</b> 2 (1 stroke; 1 systemic tuberculosis)(0.3%) <b>PBO+MTX:</b> 1 (respiratory failure)(0.4%)
<b>Bijlsma; EULAR</b>	TCZ (8 mg/kg IV /4 w)	<b>NA</b>	“no clear	“no clear	<u>Deaths:</u> 0

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2015 U-ACT-EARLY STRATEGY STUDY [1b](8)	MTX (started at 10 mg/w and increased with 30 mg/w until remission or dose-limiting toxicity) TCZ+MTX HCQ could be added.	differences among arms in terms of serious infections”	differences among arms in terms of serious adverse events”
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**Supplementary Table 3. Clinical and biological biomarkers that have been predictively associated with primary failure, therapeutic response, or remission achievement in patients treated with a first-line csDMARD.**

	DMARD therapy	Predictive/associated with response or remission	Not predictive/not associated with response or remission
<b>BMI /obesity</b>	<b>MTX mono</b>	Lower remission/LDA with higher BMI (n=3) (19–21)	
	<b>Combination</b>	Lower remission with higher BMI (19)	DAS28 (22)
<b>Male</b>	<b>MTX mono</b>	Higher response (23) Higher remission (21)	Response (24)
	<b>Combination</b>	Higher remission rate with combo vs mono (25)	
<b>Young age</b>	<b>MTX mono</b>	Requirement to bDMARD (26) Higher response (23)	Remission (21) Response (24)
	<b>Combination</b>	<50-year-old had lower remission rate with combo vs mono(25)	NA
<b>Current smoking</b>	<b>MTX mono</b>	Lower response (n=2) and higher probability of step-up therapy (n=1) (23,27–29)	Response (30)
	<b>Combination</b>	Lower response (31)	Response (30)
<b>High CRP</b>	<b>MTX mono</b>	Higher probability of bDMARD therapy: (26)	Response (5)
	<b>Combination</b>	NA	NA
<b>ACPA +</b>	<b>MTX mono</b>	Higher remission (21)* Lower response (32)	Response (n=3) (23)(33)*(34) bDMARD requirement (n=2) (26)(35)§
	<b>Combination</b>	Higher remission rate with combo vs monotherapy (25)	Response: (34)
<b>RF+</b>	<b>MTX mono</b>	NA	Response (n=3): (23)(24)(33)*, bDMARD requirement (n=2)(26)(35)§
	<b>Combination</b>	Higher remission rate with combo vs monotherapy (25)	Similar benefit with combo vs mono (36)§
<b>Cytokines chemokines</b>	<b>MTX mono</b>	TNF-alpha (37)*; TNF-alpha RI, IL-6, VCAM (38) § ; CXCL13 (39) §; CCL19 (40) §	TNF-alpha (33)* Soluble TNF-alpha R2 (41)§ IL-6, IL-1β, IL-1Ra, IL-4, IL-5, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, G-CSF, GM-CSF, IFN-γ, VEGF, CCL2 and CCL4 (33)* ; CCL2, CXCL10(40)§; S100A4(42)*
	<b>Combination</b>	NA	NA
<b>Genes</b>	<b>MTX mono</b>	<u>Folate pathways:</u> RFC1 (rs1232027) (43)**; ATIC (rs2372536)(24); MTHFR (rs1801133, rs1801131) (24); AMPD1 (rs17602729), ITPA (24) <u>Others:</u> TLR4 (44) §***; HLA-DRB1*0405 (32)*; HLA-DRB1*0101(32)*; HLA-DRB1*0301 (rs4678) (45)§§; HLA-G 14-bp (46)§; OLIG3/TNFAIP3 locus and PTPN22 (47)§; ABCB1, TNF-alpha, PTPRC and STAT4 (45) §§	<u>Folate pathways:</u> RFC1 (rs1232027)(24); ATIC (rs2372536)(n=2) (45)§§; (43)**; MTHFR (rs1801133 and rs1801131 (45)§§; GGH, DHFR, TS SNPs : (43)** <u>Others:</u> Many genes explored with negative results not detailed.
	<b>Combination</b>	Folate pathway, SLC19A1, MTR and TYM (48) § TNFb1(49)§	TLR4 Not associated with remission (44)§***
<b>Immune cells</b>	<b>MTX mono</b>	FccRIIIa/CD16 on CD14++ monocytes (50)§ Naive T cell (51)#	
	<b>Combination</b>	Synovial lymphocyte aggregates (52)	NA



<b>Others</b>	<b>MTX mono</b>	Absence of response to 2-week GC (53) ; In-vitro effect of MTX on GC receptors (54)§; 11 endogenous metabolites (55); Chromosome conformational signatures with EpiSwitch™ array (56)§	Peripheral blood gene expression patterns (57)§
	<b>Combination</b>	Absence of response to 2w GC (53)	

AMPD1: adenosine monophosphate deaminase; ATIC: 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase; bDMARD: biologic DMARD; CHST11: carbohydrate sulfotransferase 11; DHFR: dihydrofolate reductase; GGH: gamma-glutamyl hydrolase; ITPA: inosine triphosphate pyrophosphatase; RCF1: Reduced folate carrier 1; TS: thymidylate synthase. \* csDMARD monotherapy, mostly MTX; \*\* transversal studies; \*\*\* sulfasalazine (not MTX); § univariate analysis; § no correction for multiple tests applied . # pilot study + confirmation study by the same team.

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**Supplementary Table 4. Association of body mass index and smoking with therapeutic response to a first-line DMARD.**

Study	Trial	Outcome	Drug	Predictor	Sens	Spec	PPV	NPV	Multivariable OR (95% CI)
<b>Heimans 2013(19)</b>	BeSt	DAS<2.4 at 2 years	MTX or MTX+IFX or csDMARD combination	BMI ≥25 kg/m <sup>2</sup> (n=291/507)	NA	NA	NA	NA	RR=0.8 (0.6-1.0)*
<b>Sandberg 2014(20)</b>	EIRA	DAS28<2.6 at 6 months	DMARD (93% including 86% of MTX)	BMI ≥25 kg/m <sup>2</sup> (n=240/495)	NA	NA	NA	NA	0.6 (0.4-0.9)
<b>Wevers-De Boer 2012(21)</b>	IMPROVED	DAS remission at 4 months	MTX+GC	BMI as continuous variable (n=596)	NA	NA	NA	NA	0.9 (0.9-1.0)* / unit of BMI
<b>Mirpourian 2014(22)</b>	-	EULAR non-response at 6 months	MTX+HCQ+GC	BMI ≥25 kg/m <sup>2</sup> (n=82/106)	94%	75%	43%	87%	NA
<b>Saevarsdottir 2011(23)</b>	EIRA	Good EULAR response at 3 months	MTX	Current smoker vs non-smoker (n=225/n=485)	34%	73%	71%	37%	0.6 (0.4–0.9)*
<b>Saevarsdottir 2011(58)</b>	SWEFOT	EULAR response at 3 months	MTX	Current smoker vs non-smoker (n=82/n=240)	NA	NA	NA	NA	0.3 (0.2-0.6)*
<b>Teitsma 2015(28)</b>	U-ACT-EARLY	Primary failure to MTX (addition of TCZ)	MTX	Current smoker vs non-smoker (total n=108)	NA	NA	NA	NA	NA
<b>Rojas-Serrano 2011(31)</b>	-	ACR50 response at 6 months	MTX+SSZ	Current smoker vs non-smoker (n=22/n=107)	27%	90%	68%	62%	3.9 (1.4–10.8)**
<b>Maska 2012(30)</b>	TEAR	Good EULAR response at 48 weeks	csDMARD combination or MTX or MTX+ETN	Current smoker vs non-smoker (n=119/n=293)	26%	69%	38%	56%	NA
<b>Wessels 2007(29)</b>	BeSt	DAS <2.4 at 6 months	MTX	Smoker vs non-smoker (n=74/n=112)	46%	68%	62%	53%	NA

csDMARD: conventional synthetic DMARD; ETN: etanercept; MTX: methotrexate; PPV: predictive positive value; NPV: negative predictive value; sens: sensitivity; spe: specificity; SSZ: sulfasalazine.



## Research questions.

### I. Non-pharmacological management

#### A. DMARDs Adherence

What is the RR (OR) of patients with early arthritis using strategies to promote DMARDs adherence in comparison to those non using such strategies, with respect to clinical, functional and radiologic outcome (disease activity, HAQ disability and radiographic progression) after x months/years of follow up?

Population: patients with early arthritis

Intervention: random allocation of any strategy to promote adherence to DMARDs

Comparison: patients with early arthritis for whom strategies to promote DMARDs adherence are applied vs those for whom strategies to promote DMARDs adherence have not been applied

Outcome:

- Disease activity:
  - Mean (SD) or median (IQR) difference in variations of disease activity (DAS / DAS28, SDAI / CDAI, ) at x months/years between the 2 groups
- Function:
  - Mean (SD) or median (IQR) difference in variations of physical function (HAQ-score) at x months/year(s) between the 2 groups
- Structural:
  - Percentage of patients (per group or as OR/RR) with radiographic progression after x months/years
  - Mean (SD) or median (IQR) difference in variations of Sharp score (including modifications) or Larsen score (including modifications) at x months/year(s) between the 2 groups

Type of study: RCT

#### B. Coping Strategies

What is the efficacy (in terms of pain, disease activity, physical function or health related quality of life) of coping strategies in early arthritis patients?

Population: Patients with early arthritis

Intervention:i) evaluation of coping strategies;

Comparison: i) Patients with early arthritis that use coping strategy A vs patients with early arthritis that use coping strategy B

Outcome:

- Disease activity:

- Mean (SD) or median (IQR) difference: - of pain decrease (VAS) at x months/years between the 2 groups - in variations of disease activity (DAS / DAS28, SDAI / CDAI) at x months/years between the 2 groups

- Function:

- Mean (SD) or median (IQR) difference in variations of physical function (HAQ-score) at x months/years between the 2 groups

- Quality of life:

- Mean (SD) or median (IQR) difference in variations of HRQoL at x months/years between the 2 groups

Type of study: i) Prospective studies ii) RCT

### C. Psychological interventions

What is the efficacy (in terms of pain, disease activity, physical function or health related quality of life) of psychological intervention in patients with chronic persistent arthritis?

Patients: Patients with early arthritis

Intervention: use of psychological interventions

Comparison: Patients with early arthritis for whom psychological interventions have been applied vs those in whom psychological interventions have not been applied

Outcome:

- Disease activity:

- Mean (SD) or median (IQR) difference: - of pain decrease (VAS) at x months/years between the 2 groups - in variations of disease activity (DAS / DAS28, SDAI / CDAI) at x months/years between the 2 groups

- Function:

- Mean (SD) or median (IQR) difference in variations of physical function (HAQ-score) at x months/years between the 2 groups

- Quality of life:

- Mean (SD) or median (IQR) difference in variations of HRQoL at x months/years between the 2 groups

Type of study: i) Prospective studies. ii) RCTs

#### D. Exercise

What is the efficacy (in terms of pain, morning stiffness, disease activity, physical function or health related quality of life) of exercise therapy in early persistent arthritis patients?

Population: Patients with early persistent arthritis for whom exercise therapy has been prescribed

Intervention: random allocation of exercise therapy

Comparison: Patients with early persistent arthritis receiving the same pharmacological treatment but for whom exercise therapy has not been prescribed

Outcome:

- Disease activity:
  - Percentage of patients (per group or as OR/RR) with clinical remission after x months/years
  - Mean (SD) or median (IQR) difference: - of pain decrease (VAS) at x months/years between the 2 groups - in variations of disease activity (DAS / DAS28, SDAI / CDAI,) at x months/years between the 2 groups
- Function:
  - Mean (SD) or median (IQR) difference:
    - in variations of physical function (HAQ-score) at x months/years between the 2 groups.
    - in variations of length of morning stiffness at x months/years between the 2 groups
- Structural:
  - Mean (SD) or median (IQR) difference in variations of Sharp score (including modifications) or Larsen score (including modifications) at x months/years between the 2 groups
  - Percentage of patients (per group or as OR/RR) with radiographic progression after x months/years

Type of study: RCT

#### E. Smoking cessation

What is the RR (OR) for patients with early arthritis who quit smoking in comparison those who will maintain smoking with respect to disease activity, HAQ disability and/or radiographic progression after x month(s)/year(s)?

Population: patients with early arthritis who quit smoking

Intervention: None

Control: Patients with early arthritis who maintain smoking

Outcome:

- Disease activity:
  - Mean (SD) or median (IQR) difference in variations of disease activity (DAS / DAS28, SDAI / CDAI) at x months/years between the 2 groups
  
- Function:
  - Mean (SD) or median (IQR) difference in variations of physical function (HAQ-score) at x months/year(s) between the 2 groups
  
- Structural:
  - Percentage of patients (per group or as OR/RR) with radiographic progression after x months/years
  - Mean (SD) or median (IQR) difference in variations of Sharp score (including modifications) or Larsen score (including modifications) at x months/year(s) between the 2 groups

Type of study: Prognostic studies with prospective follow-up

## II. NSAID

1) What is the difference of pain release in patients with early arthritis taking NSAIDs compared with those only taking simple analgesics?

Population: patients with early arthritis

Intervention: random allocation of NSAIDs vs simple analgesics

Comparison: patients with early arthritis taking NSAID vs those not taking NSAIDS but simple analgesics

Outcome: mean (SD) or median (IQR) difference between the 2 groups at x days/months of

- pain decrease

- DAS28

Type of study: RCT

2) What is the RR (OR) of adverse events in patients with early arthritis taking NSAIDs compared with those taking simple analgesics?

Population: patients with early arthritis

Intervention: random allocation of NSAIDs or simple analgesics

Comparison: patients with early arthritis taking NSAID vs those not taking NSAIDS but simple analgesics

Outcome: RR (OR or percentage of patients in each group) of serious adverse events (*digestive perforated peptic ulcers* and *bleeding peptic ulcers*, renal failure, cardiovascular events), death and withdrawal at x months between the 2 groups

Type of study: RCT

### III. Glucocorticoids

1) What is the RR (OR) to obtain therapeutic response, remission or radiographic non-progression at x year(s) in patients with early arthritis taking systemic glucocorticoids (GC) compared with those not taking GC?

Population: patients with early arthritis

Intervention: random allocation of systemic GC (oral, IM or IV)

Comparison: patients with systemic GC vs without GC

Outcome:

- response: OR/RR of responders (EULAR-response criteria, ACR response criteria (20/50/70) at x months between the 2 groups
- disease activity: difference in variations of disease activity (DAS / DAS28, SDAI / CDAI) at x months between the 2 groups; OR/RR of remission (ACR/EULAR, SDAI or DAS28) at x months/year(s) between the 2 groups

- function: difference in variations of physical function (HAQ-score) at x months/year(s) between the 2 groups
- structural: OR/RR of radiographic progression at x year(s) between the 2 groups; difference in variations of Sharp score (including modifications) or Larsen score (including modifications) at x year(s) between the 2 groups

Type of study: RCT

2) What is the RR (OR) to obtain therapeutic response, remission or radiographic non-progression at x year(s) in patients with early arthritis taking prolonged oral GC compared with those having parenteral GC boosts (IM or IV)?

Population: patients with early arthritis

Intervention: random allocation of GC route (prolonged oral GC compared or parenteral GC boosts)

Control or Comparison: patients with early arthritis taking prolonged oral GC compared with those having parenteral GC boosts (IM or IV)

Outcome:

- response: OR/RR of responders (EULAR-response criteria, ACR response criteria (20/50/70) at x months between the 2 groups
- disease activity: difference in variations of disease activity (DAS / DAS28, SDAI / CDAI) at x months between the 2 groups; OR/RR of remission (ACR/EULAR, SDAI or DAS28) at x months/year(s) between the 2 groups
- function: difference in variations of physical function (HAQ-score) at x months/year(s) between the 2 groups

Type of study: RCT

3) What is the RR (OR) to obtain remission at x year(s) in patients with early arthritis having intraarticular GC injections compared with those not taking GC?

Population: patients with early arthritis

Intervention: random allocation of intraarticular GC

Comparison: patients with intraarticular GC vs without GC

Outcome:

- disease activity: difference in variations of disease activity (DAS / DAS28, SDAI / CDAI) at x months between the 2 groups; OR/RR of remission (ACR/EULAR, SDAI or DAS28) at x months/year(s) between the 2 groups

Type of study: RCT

4) What is the RR (OR) of adverse events in patients with early arthritis taking systemic GC compared with those not taking steroids?

Population: patients with early arthritis

Intervention: random allocation of systemic (oral, IV, IM) GC

Comparison: patients with early arthritis taking systemic GC vs those not taking GC

Outcome: RR (OR or percentage of patients in each group) of any adverse event (diabetes, dyslipidemia, cardiovascular events, infections, osteoporosis, etc.), severe AE and death between the 2 groups

Type of study: RCT

5) What is the RR (OR) of adverse events in patients with early arthritis taking prolonged oral GC compared with those having GC boosts (IM or IV)?

Population: patients with early arthritis

Intervention: random allocation of GC route

Comparison: patients with early arthritis taking with early arthritis taking prolonged oral GC vs those having GC boosts (IM or IV)

Outcome: RR (OR or percentage of patients in each group) of any adverse event (diabetes, dyslipidemia, cardiovascular events, infections, osteoporosis, etc.), severe AE and death between the 2 groups

Type of study: RCT

#### IV. DMARDs

1) What is the RR (OR) to obtain therapeutic response, remission or radiographic non-progression at x months/year(s) in patients with early arthritis taking intensive treatment (combination of csDMARDs, tsDMARD or bDMARD ab initio) compared with less intensive therapy (csDMARD monotherapy)?

Population: patients with early arthritis

Intervention: random allocation of intensive treatment

Comparison: patients with early arthritis taking intensive treatment (combination csDMARDs [including MTX, SSZ, HCQ, LEF] or bDMARD ab initio) vs those not taking intensive treatment (csDMARDs monotherapy)

Outcomes:

response: OR/RR of responders (EULAR-response criteria, ACR response criteria (20/50/70) at x months between the 2 groups; retention rate

disease activity: difference in variations of disease activity (DAS / DAS28, SDAI / CDAI) at x months between the 2 groups; OR/RR of remission (ACR/EULAR, SDAI or DAS28) at x months/year(s) between the 2 groups

function: difference in variations of physical function (HAQ-score) at x months/year(s) between the 2 groups

structural: OR/RR of radiographic progression at x year(s) between the 2 groups; difference in variations of Sharp score (including modifications) or Larsen score (including modifications) at x year(s) between the 2 groups

Type of study: RCT

2) What is the RR (OR) of adverse events with early arthritis taking intensive treatment (combination csDMARDs, tsDMARD or bDMARD ab initio) compared with less intensive therapy (conventional csDMARD monotherapy)?

Population: patients with early arthritis

Intervention: random allocation of intensive treatment

Comparison: patients with early arthritis taking intensive treatment (combination csDMARDs [including MTX, SSZ, HCQ, LEF] or bDMARD ab initio) vs those not taking intensive treatment (csDMARDs monotherapy)

Outcomes: OR/RR of any adverse event (infections, liver disorders, cytopenia, neoplasia, teratogenicity, renal failure, cardiovascular event), serious AE, death and withdrawal between the 2 groups

Type of study: RCT

3) What is the sensitivity/specificity (or PPV/NPV) of any tools to predict AT BASELINE non-response to a first csDMARD strategy in patients with early arthritis?

Population: patients with early arthritis with non-response (EULAR-response criteria, ACR response criteria (20/50/70)) at x months to a first csDMARD strategy (MTX, LEF, SLZ or csDMARD combination)



Intervention: any tools at baseline (RF/ACPA tests, DAS28, CRP, ESR, HAQ, radiographic damage, new biomarkers, multimarker test, etc.)

Control: patients with early arthritis with response (EULAR-response criteria, ACR response criteria (20/50/70) at x months to a first csDMARD strategy (MTX, LEF, SLZ or csDMARD combination)

Outcome: Sensitivity/specificity or PPV/NPV (and 2-by-2 table with crude numbers) or OR/RR of non-response depending on positivity or negativity of the predictive tools

Type of study: prognostic study with prospective follow-up

3) What is the RR (OR) of patients meeting remission or with radiographic non-progression when DMARD is started within x weeks compared when DMARD is started beyond x weeks of symptom duration?

Population: patients with early arthritis that have been treated with DMARD within x weeks after symptom duration

Intervention: DMARD therapy

Control: patients with early arthritis that have been treated with DMARD beyond x weeks after symptom duration

Outcome:

- disease activity: difference in variations of disease activity (DAS / DAS28, SDAI / CDAI) at x months between the 2 groups; OR/RR of remission (ACR/EULAR, SDAI or DAS28) at x months/year(s) between the 2 groups
- function: difference in variations of physical function (HAQ-score) at x months/year(s) between the 2 groups
- structural: OR/RR of radiographic progression at x year(s) between the 2 groups; difference in variations of Sharp score (including modifications) or Larsen score (including modifications) at x year(s) between the 2 groups

Type of study: prognostic study with prospective follow-up

4) What is the optimal symptom duration threshold with the best Youden index or sensitivity/specificity or area under the curve to instaurate therapy and obtain clinical remission and/or radiographic non-progression at x months in patients with early arthritis?

Population: patients with early arthritis achieving clinical remission or radiographic non-progression during x years of follow-up

Intervention: csDMARD introduction

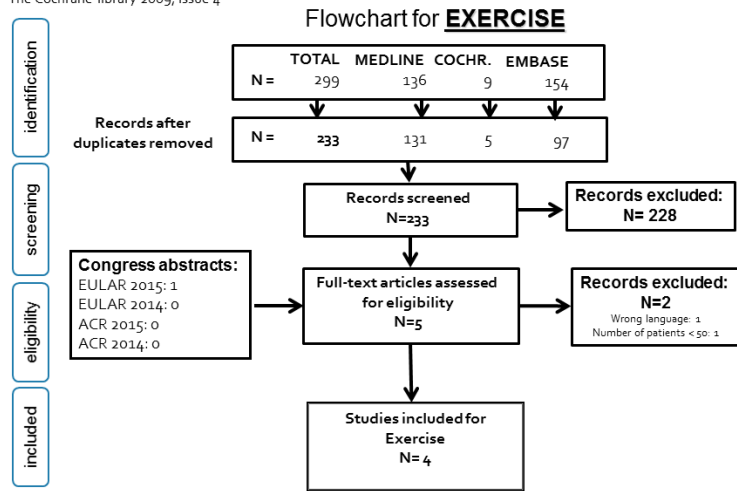
Control: patients with early arthritis with persistent arthritis or radiographic progression during x years of follow-up

Outcome: symptom duration associated with the best youden index or area under the curve or sensitivity/specificity to obtain clinical remission, DMARD-free remission and non-radiographic progression

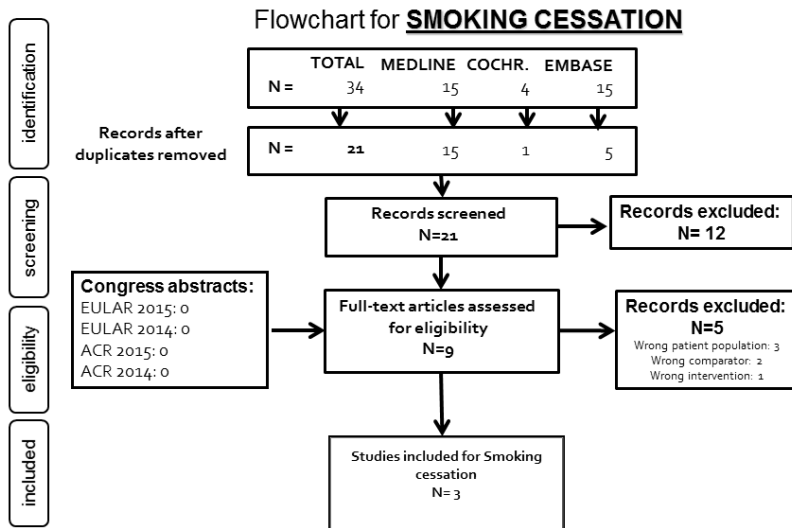
Type of study: prognostic study with prospective follow-up

## Flowcharts

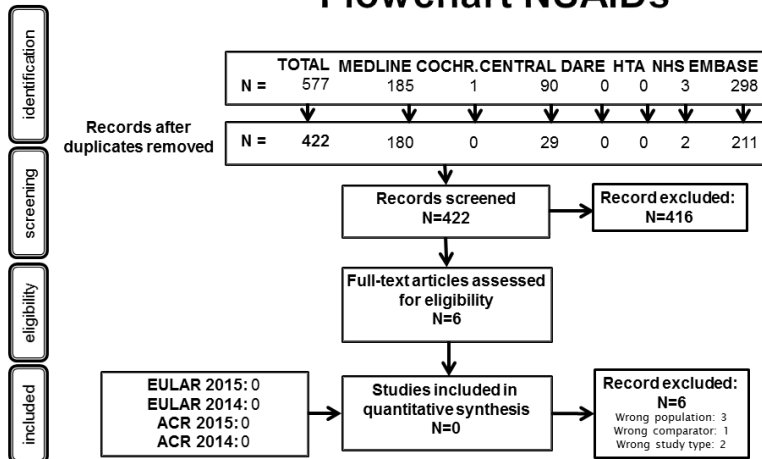
SLR conducted from december 2008 to October 30, 2015. Existing SLR up to december 2008: Hurkmans E. et al. The Cochrane library 2009; issue 4



SLR conducted from 2005 to October 30, 2015

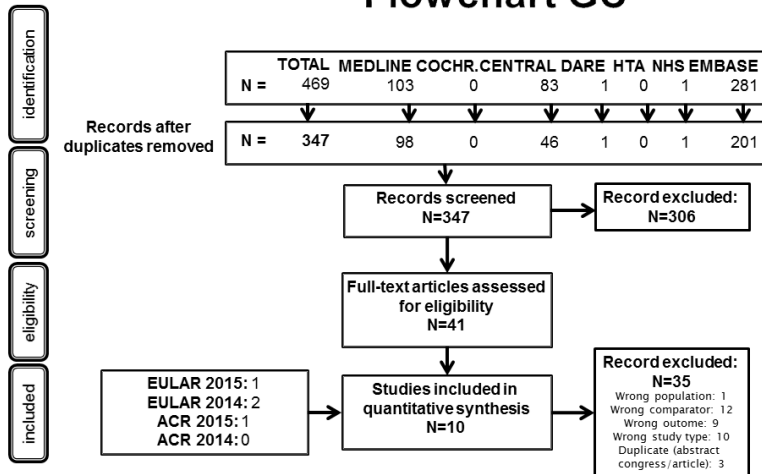


## Flowchart NSAIDs



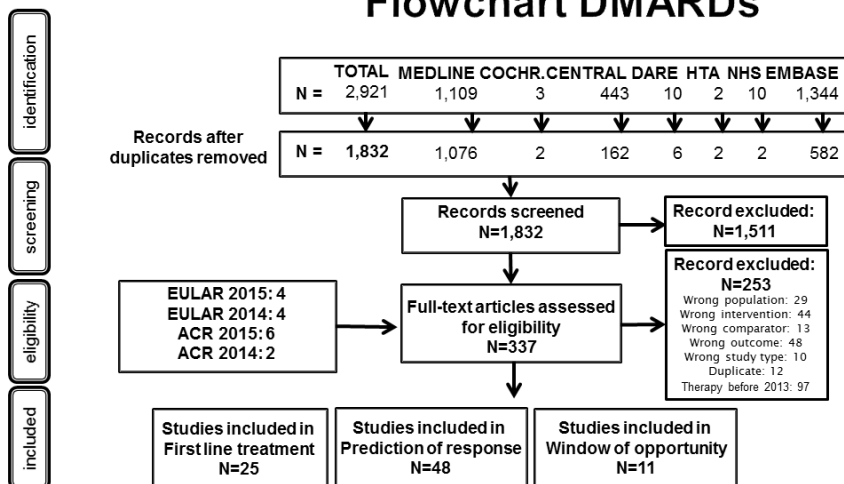
SLR conducted from 2005 to November 2015. Existing SLR: Combe B et al. Ann Rheum Dis 2007;66:34-45.

## Flowchart GC



SLR conducted from 2013 to November 2015 Existing SLR: Gaujoux-Viala C et al. Ann Rheum Dis 2014;73:510-515.

## Flowchart DMARDs



SLR conducted from 2013 to November 2015 for first line treatment and window of opportunity and from 2005 to November 2015 for prediction of response. Existing SLR: Gaujoux-Viala C et al. Ann Rheum Dis 2014;73:510-515; Combe B et al. Ann Rheum Dis 2007; 66:34-45

## Research strategies.

### I. Non-pharmacological management

#### DMARDs Adherence

#### Research strategy

#### MEDLINE

1. exp Arthritis, Rheumatoid/
2. exp early diagnosis/
3. 1 and 2
4. exp Arthritis, Rheumatoid/ and (early or recent).tw.
5. ((early or recent\$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.
6. or/3-5
7. Antirheumatic Agents/
8. Antirheumatic\$.tw.
9. dmard\$.tw.
10. disease modifying antirheumatic\$.tw.
11. Methotrexate/
12. Methotrexate.tw.
13. (Abitrexate or amet?opterine or Abitrexate or A Met?opterine\$ or Antifolan or Emt?exate or Enthexate or Farnitrexate or Folex or Ledertrexate or Methoblastin or Methohexate or Methotrate or Methylaminopterin or Metotrexat\$ or mtx or Novatrex or Rheumatrex).tw.
14. exp Isoxazoles/
15. isoxazole\$.tw.
16. leflunomide\$.tw.
17. (Afiancen or Arabloc or Arava or Artrilab or Artrimod or Filartros or Immunoartro or Lefluar or Leflucross or Lefno or Lefra or Lefumide or Lisifen or Molagar or Repso or Rumalef).tw.
18. Sulfasalazine/
19. sulfasalazine.tw.



40. (cyclophosph\$ or cytophosphan or Cytoxan or sendoxan or endoxan or neosar or nsc-26271 or procytox or b-518 or ifosfamide or isophosphamide or iphosphamide or isofosfamide or holoxan or nsc-109\$ or asta z 4942 or cfx or phosphoramid mustard\$).tw.

41. Mycophenolic Acid/

42. mycophenolate.tw.

43. (Arzip or Baxmune or CellCept or Cellmune or Celprot or Ceptolate or Imulate or Imuxgen or Lanfetil or Limfocept or Metocris or Micocept or MMF or Mofecept or Mofetyl or Mofilel or Mofimutral or Mometil or Mophecen or Munotras or Myaccord or Mycept or Myclausenor or Mycofenor or Mycolat or Mycoldosa or Mycophen or Myfenax Myfetil or Mygref or Myotec or Mysept or Presumin or Refrat or Renocell or Supresta or Tevacept or Trixin).tw.

44. exp Chlorambucil/

45. chlorambucil.tw.

46. (Amboclorin or Clokeran or Leukeran or Linfolysin or Lympholysin).tw.

47. Minocycline/

48. minocyclin\$.tw.

49. (Acneclin or Akamin or Aknemin or Akne-Puren or Aknereduct or Aknin-Mino or Aknin-N or Aknoral or Aknosan or Apominolin or Arestinor or Auramin or Blemix or Borymycin or Cipancin or Cyclimycin or Dentomycin\$ or durakne or Dynacin or Enca or Icht-Oralor or Klinoc or Klinomycin or Klinotab or Lederderm or Logryx or Meibi or Mestacine or Micromycin or Minac 50 or Minakne or Minaxen or Mino-50 or Minocin or Minoclin or Minodene or Minoderm or Minogalen or Minolis or Minomax or Minomycin or Minoplus or Minosil or Minostad or Minotab\$ or Minotekor or Minotrex or Minotyrol or Mino-Wolff or Minox or Mynocine or Myrac or Oracyclin or Parocline or Periocline or Peritrol or Ranmino or Romin or Seboclear or Sebomin or Sebren or Skid or Skinocyclin or Solodyn or Spicline or Triomin or Udimin or Vectrin or Yelnac or Zacnan).tw.

50. Pyrroles/

51. tofacitinib.tw.

52. Xeljanz.tw.

53. or/7-52

54. exp Patient Compliance/

55. Treatment Refusal/

56. (adhere\$ or nonadhere\$ or comply\$ or complianc\$ or noncompliant\$ or persist\$ or continu\$ or discontinu\$).tw.

57. or/54-56

58. and/6,53,57

59. (animals not (humans and animals)).sh.

60. 58 not 59



61. limit 60 to (english language and yr="2005 -Current")

### The Cochrane Library

- #1 MeSH descriptor: [Antirheumatic Agents] explode all trees
- #2 Antirheumatic\*:ti,ab
- #3 dmard\*:ti,ab
- #4 "disease modifying antirheumatic\*":ti,ab
- #5 MeSH descriptor: [Methotrexate] this term only
- #6 Methotrexate:ti,ab
- #7 (Abitrexate or amet?opterine or Abitrexate or A Met?opterine\* or Antifolan or Emt?exate or Enthexate or Farmitrexate or Folex or Ledertrexate or Methoblastin or Methohexate or Methotrate or Methylaminopterin or Metotrexat\$ or mtx or Novatrex or Rheumatrex):ti,ab
- #8 MeSH descriptor: [Isoxazoles] explode all trees
- #9 isoxazole\*:ti,ab
- #10 leflunomide\*:ti,ab
- #11 (Afiancen or Arabloc or Arava or Artrilab or Artrimod or Filartros or Inmunoartro or Lefluar or Leflucross or Lefno or Lefra or Lefumide or Lisifen or Molagar or Repso or Rumalef):ti,ab
- #12 MeSH descriptor: [Sulfasalazine] this term only
- #13 sulfasalazine:ti,ab
- #14 (Salazosulfapyridine or sulfasalazine or Sulfosalazine or Sulfasal?zine or Salazopyridin\* or asulfidine or azulf?dine):ti,ab
- #15 MeSH descriptor: [Hydroxychloroquine] this term only
- #16 Hydroxychloro\*:ti,ab
- #17 (Axokineor or Dolquine or Ercoquin or Evoquin or HCQS or HQT or Hydrocad or Hydroquin or Ilinol or Immard or Metirel or Narbon or Oxcq or Oxiklorin or Oxy-Q or Plaquen?l or Polirreuminor or Quensyl or Reuquinol):ti,ab
- #18 MeSH descriptor: [Gold Compounds] explode all trees
- #19 MeSH descriptor: [Organogold Compounds] explode all trees
- #20 gold:ti,ab
- #21 MeSH descriptor: [Chloroquine] explode all trees
- #22 chloroquine\*:ti,ab
- #23 (aralen or arechine or arequin or chingamin or chlorochin or khingamin or nivaquine or oxychloroquine or oxychlorochin or plaquinol or plaquinil or quensy or anoclor or arthrabas

or avloclor or cidanchin or clopirim or collagenan or daraclor or daramal or dichinalex or difosquin or diroquine or genocin or heliopar or klorokin or malarex or malaviron or mirquin or nivaquine or novo-chloroquine or novochloroquine or paluken or palux or pharmaquinine or plasmquine or promal or p-roquine or resoquin\$ or savarine or syncoquin or weimerquin):ti,ab

#24 MeSH descriptor: [Azathioprine] this term only

#25 azathioprine:ti,ab

#26 (Aseroprim or Aseroprin or Azaallen or Azadus or Azafalk or Azafor or Azafrine or Azaglux or Azahexal or Aza?mun\* or Azamedac or Azap or Azap?in\* or Azapress or Aza-Q or Azarek or Azasan or Azathiodura or Azathiodura or Azathioregio or Azatrilem or Azimune or Azop?in\* or Azoran or Berkaprime or Colinsan or Glaxoprin or Immunoprin or Imuger or Imunen or Imuprin\$ or Imuran or Imure? or Imuzat or Oprisine or Satedon or Thioprine or Tiosalprin or Transimune or Zaprine or Zytrim):ti,ab

#27 MeSH descriptor: [Cyclosporins] explode all trees

#28 c?closporin\*:ti,ab

#29 (neoral or gengraf or restasis or sandimmun\* or sangcya):ti,ab

#30 MeSH descriptor: [Penicillamine] explode all trees

#31 Penicillamine:ti,ab

#32 (Adalkenor or Artamin or Atamir or Byanodine or Cilamin or Cuprenil or Cuprimine or Cupripen or Depen or Distamin\* or D-Penaminate or Gerodyl or Kelatin\* or Mercaptyl or Metalcaptase or Pendramine or Rhumantim or Sufortan\* or Trisorcin or Trolovol):ti,ab

#33 MeSH descriptor: [Cyclophosphamide] explode all trees

#34 (cyclophosph\* or cytophosphan or Cytoxan or sendoxan or endoxan or neosar or nsc-26271 or procytox or b-518 or ifosfamide or isophosphamide or iphosphamide or isofosfamide or holoxan or nsc-109\* or "asta z 4942" or cfx or "phosphoramid mustard\*"):ti,ab

#35 MeSH descriptor: [Mycophenolic Acid] this term only

#36 mycophenolate:ti,ab

#37 (Arzip or Baxmune or CellCept or Cellmune or Celprot or Ceptolate or Imulate or muxgen or Lanfetil or Limfocept or Metocris or Micocept or MMF or Mofecept or Mofetyl or Mofilem or Mofimutrat or Mometil or Mophecen or Munotras or Myaccord or Mycept or Myclausenor or Mycofenor or Mycolat or Mycoldosa or Mycophen or Myfenax Myfetil or Mygref or Myotec or Mysept or Presumin or Refrat or Renocell or Supresta or Tevacept or Trixin):ti,ab

#38 MeSH descriptor: [Chlorambucil] explode all trees

#39 chlorambucil:ti,ab

#40 (Amboclorin or Clokeran or Leukeran or Linfolysin or Lympholysin):ti,ab

#41 MeSH descriptor: [Minocycline] this term only

#42 minocyclin\*:ti,ab

- #43 (Acneclin or Akamin or Aknemin or Akne-Puren or Aknereduct or Aknin-Mino or Aknin-N or Aknoral or Aknosan or Apominolin or Arestinor or Auramin or Blemix or Borymycin or Cipancin or Cyclimycin or Dentomyacin\* or durakne or Dynacin or Enca or Icht-Oralor or Klinoc or Klinomyacin or Klinotab or Lederderm or Logryx or Meibi or Mestacine or Micromycin or "Minac 50" or Minakne or Minaxen or Mino-50 or Minocin or Minoclin or Minodene or Minoderm or Minogalen or Minolis or Minomax or Minomyacin or Minoplus or Minosil or Minostad or Minotab\* or Minotekor or Minotrex or Minotyrol or Mino-Wolff or Minox or Mynocine or Myrac or Oracyclin or Parocline or Periocline or Peritrol or Ranmino or Romin or Seboclear or Sebomin or Sebren or Skid or Skinocyclin or Solodyn or Spicline or Triomin or Udimia or Vectrin or Yelnac or Zacnan):ti,ab
- #44 MeSH descriptor: [Pyrroles] this term only
- #45 tofacitinib:ti,ab
- #46 Xeljanz:ti,ab
- #47 #1 or #2 or #3 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46
- #48 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
- #49 MeSH descriptor: [Early Diagnosis] explode all trees
- #50 #48 and #49
- #51 (early or recent):ti,ab
- #52 #48 and #51
- #53 ((early or recent\* or undifferentiated or persistent or unclassified) near/3 arthritis):ti,ab
- #54 #50 or #52 or #53
- #55 MeSH descriptor: [Patient Compliance] explode all trees
- #56 MeSH descriptor: [Treatment Refusal] this term only
- #57 (adhere\* or nonadhere\* or comply\* or complianc\* or noncomplan\* or persist\* or continu\* or discontinue\*):ti,ab
- #58 #55 OR #56 OR #57
- #59 #47 and #54 AND #58 Publication Year from 2005 to 2015

## EMBASE

- #56. #55 AND [humans]/lim AND [english]/lim AND [embase]/lim AND AND ([adolescent]/lim OR [adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py) AND ('Article'/it OR 'Article in Press'/it)

#55. #50 AND #54

#54. #51 OR #52 OR #53

#53. adhere\*:ab,ti OR nonadhere\*:ab,ti OR comply\*:ab,ti OR complianc\*:ab,ti OR  
noncompliant\*:ab,ti OR persist\*:ab,ti OR ontinu\*:ab,ti OR discontinue\*:ab,ti

#52. 'treatment refusal'/de

#51. 'patient compliance'/exp

#50. #6 AND #49

#49. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19  
OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31  
OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43  
OR #44 OR #45 OR #46 OR #47 OR #48

#48. xeljanz:ab,ti

#47. tofacitinib:ab,ti

#46. acneclin:ab,ti OR akamin:ab,ti OR aknemin:ab,ti OR 'akne puren':ab,ti OR aknereduct:ab,ti OR  
'aknin mino':ab,ti OR 'aknin n':ab,ti OR aknoral:ab,ti OR aknosan:ab,ti OR apominolin:ab,ti OR  
arestinor:ab,ti OR auramin:ab,ti OR blemix:ab,ti OR borymycin:ab,ti OR cipancin:ab,ti OR  
cyclimycin:ab,ti OR dentomyacin\*:ab,ti OR durakne:ab,ti OR dynacin:ab,ti OR enca:ab,ti OR 'icht  
oralor':ab,ti OR klinoc:ab,ti OR klinomyacin:ab,ti OR klinotab:ab,ti OR lederderm:ab,ti OR  
logryx:ab,ti OR meibi:ab,ti OR mestacine:ab,ti OR micromycin:ab,ti OR 'minac 50':ab,ti OR  
minakne:ab,ti OR minaxen:ab,ti OR 'mino 50':ab,ti OR minocin:ab,ti OR minoclin:ab,ti OR  
minodene:ab,ti OR minoderm:ab,ti OR minogalen:ab,ti OR minolis:ab,ti OR minomax:ab,ti OR  
minomyacin:ab,ti OR minoplus:ab,ti OR minosil:ab,ti OR minostad:ab,ti OR minotab\*:ab,ti OR  
minotekor:ab,ti OR minotrex:ab,ti OR minotyrol:ab,ti OR 'mino wolff':ab,ti OR minox:ab,ti OR  
mynocine:ab,ti OR myrac:ab,ti OR oracyclin:ab,ti OR parocline:ab,ti OR periocline:ab,ti OR  
peritrol:ab,ti OR ranmino:ab,ti OR romin:ab,ti OR seboclear:ab,ti OR sebomin:ab,ti OR  
sebren:ab,ti OR skid:ab,ti OR skinocyclin:ab,ti OR solodyn:ab,ti OR spicline:ab,ti OR triomin:ab,ti  
OR udimax:ab,ti OR vectrin:ab,ti OR yelnac:ab,ti OR zacnan:ab,ti

#45. minocyclin\*:ab,ti

#44. 'minocycline'/de

#43. ambochlorin:ab,ti OR clokeran:ab,ti OR leukeran:ab,ti OR linfolysin:ab,ti OR lympholysin:ab,ti

#42. chlorambucil:ab,ti

#41. 'chlorambucil'/de

#40. arzip:ab,ti OR baxmune:ab,ti OR cellcept:ab,ti OR cellmune:ab,ti OR celprot:ab,ti OR

ceptolate:ab,ti OR imulate:ab,ti OR muxgen:ab,ti OR lanfetil:ab,ti OR limfocept:ab,ti OR

metocris:ab,ti OR micocept:ab,ti OR mmf:ab,ti OR mofecept:ab,ti OR mofetyl:ab,ti OR  
mofilex:ab,ti OR mofimutal:ab,ti OR mometil:ab,ti OR mophecen:ab,ti OR munotras:ab,ti OR  
myaccord:ab,ti OR mycept:ab,ti OR myclausenor:ab,ti OR mycofenor:ab,ti OR mycolat:ab,ti OR  
mycoldosa:ab,ti OR mycophen:ab,ti OR myfenax:ab,ti AND myfetil:ab,ti

OR mygref:ab,ti OR myotec:ab,ti OR mysept:ab,ti OR presumin:ab,ti OR refrat:ab,ti OR  
renocell:ab,ti OR supresta:ab,ti OR tevacept:ab,ti OR trixin:ab,ti

#39. mycophenolate:ab,ti

#38. 'mycophenolic acid'/de

#37. cyclophosph\*:ab,ti OR cytophosphan:ab,ti OR cytoxan:ab,ti OR sendoxan:ab,ti OR endoxan:ab,ti  
OR neosar:ab,ti OR 'nsc 26271':ab,ti OR procytox:ab,ti OR 'b 518':ab,ti OR  
ifosfamide:ab,ti OR isophosphamide:ab,ti OR iphosphamide:ab,ti OR isofosfamide:ab,ti OR  
holoxan:ab,ti OR 'nsc 109':ab,ti OR 'asta z 4942':ab,ti OR cfx:ab,ti OR 'phosphoramide  
mustard':ab,ti OR 'phosphoramide mustards':ab,ti

#36. 'cyclophosphamide'/de

#35. adalkenor:ab,ti OR artamin:ab,ti OR atamir:ab,ti OR byanodine:ab,ti OR cilamin:ab,ti OR  
cuprenil:ab,ti OR cuprimine:ab,ti OR cupripen:ab,ti OR depen:ab,ti OR distamin\*:ab,ti  
OR 'd penamine':ab,ti OR gerodyl:ab,ti OR kelatin\*:ab,ti OR mercaptyl:ab,ti OR  
metalcaptase:ab,ti OR pendramine:ab,ti OR rhumantin:ab,ti OR sufortan\*:ab,ti OR trisorcin:ab,ti  
OR trolovol:ab,ti

#34. 'penicillamine'/de

#33. neoral:ab,ti OR gengraf:ab,ti OR restasis:ab,ti OR sandimmun\*:ab,ti OR sangcya:ab,ti

#32. cyclosporin\*:ab,ti OR ciclosporin\*:ab,ti

#31. 'cyclosporin derivative'/de

#30. aseroprim:ab,ti OR aseroprin:ab,ti OR azaallen:ab,ti OR azadus:ab,ti OR azafalk:ab,ti  
OR azafor:ab,ti OR azafrine:ab,ti OR azaglax:ab,ti OR azahexal:ab,ti OR azamun\*:ab,ti  
OR azaimun:ab,ti OR azamedac:ab,ti OR azap:ab,ti OR azapin\*:ab,ti OR azaprine\*:ab,ti OR  
azapress:ab,ti OR 'aza q':ab,ti OR azarek:ab,ti OR azasan:ab,ti OR azathiodura:ab,ti OR  
azathioregio:ab,ti OR azatrilem:ab,ti OR azimune:ab,ti OR azopin\*:ab,ti OR azoran:ab,ti OR  
berkaprine:ab,ti OR colinsan:ab,ti OR glaxoprin:ab,ti OR immunproprin:ab,ti OR imuger:ab,ti OR  
imunen:ab,ti OR imuprin\*:ab,ti OR imuran:ab,ti OR imure\*:ab,ti OR imuzat:ab,ti OR  
oprisine:ab,ti OR satedon:ab,ti OR thioprine:ab,ti OR tiosalprin:ab,ti OR transimune:ab,ti OR  
zaprine:ab,ti OR zytrim:ab,ti

#29. azathioprine:ab,ti

#28. 'azathioprine'/de

#27. aralen:ab,ti OR arechine:ab,ti OR arequin:ab,ti OR chingamin:ab,ti OR chlorochin:ab,ti OR  
khingamin:ab,ti OR oxychloroquine:ab,ti OR oxychlorochin:ab,ti OR plaquinol:ab,ti OR  
plaquinil:ab,ti OR quensy:ab,ti OR anoclor:ab,ti OR arthrabas:ab,ti OR avloclor:ab,ti OR

cidanchin:ab,ti OR clopirim:ab,ti OR collagenan:ab,ti OR daraclor:ab,ti OR daramal:ab,ti OR dichinalex:ab,ti OR difosquin:ab,ti OR diroquine:ab,ti OR genocin:ab,ti OR heliopar:ab,ti OR klorokin:ab,ti OR malarex:ab,ti OR malaviron:ab,ti OR mirquin:ab,ti OR nivaquine:ab,ti OR 'novo chloroquine':ab,ti OR novochloroquine:ab,ti OR paluken:ab,ti OR palux:ab,ti OR

pharmaquinine:ab,ti OR plasmquine:ab,ti OR promal:ab,ti OR 'p roquine':ab,ti OR resoquin\$:ab,ti OR savarine:ab,ti OR syncoquin:ab,ti OR weimerquin:ab,ti

#26. chloroquine\*:ab,ti

#25. 'chloroquine'/de

#24. gold:ab,ti

#23. 'gold therapy'/de

#22. axokineor:ab,ti OR dolquine:ab,ti OR ercoquin:ab,ti OR evoquin:ab,ti OR hcqs:ab,ti OR hqt:ab,ti OR hydrocad:ab,ti OR hydroquin:ab,ti OR ilinol:ab,ti OR immard:ab,ti OR metirel:ab,ti OR narbon:ab,ti OR oxcq:ab,ti OR oxiklorin:ab,ti OR 'oxy q':ab,ti OR plaquenil:ab,ti OR polirreuminor:ab,ti OR quensyl:ab,ti OR reuquinol:ab,ti

#21. hydroxychloro\*:ab,ti

#20. 'hydroxychloroquine'/de

#19. salazosulfapyridine:ab,ti OR sulfasalazine:ab,ti OR sulfosalazine:ab,ti OR sulfasazine:ab,ti OR sulfasizine:ab,ti OR salazopyridin\*:ab,ti OR asulfidine:ab,ti OR azulfadine:ab,ti OR azulfidine:ab,ti

#18. sulfasalazine:ab,ti

#17. 'salazosulfapyridine'/de

#16. afiancen:ab,ti OR arabloc:ab,ti OR arava:ab,ti OR artilab:ab,ti OR artrimid:ab,ti OR filartros:ab,ti OR immunoartro:ab,ti OR lefluar:ab,ti OR leflucross:ab,ti OR lefno:ab,ti OR lefra:ab,ti OR lefumide:ab,ti OR lisifen:ab,ti OR molagar:ab,ti OR repso:ab,ti OR rumalef:ab,ti

#15. isoxazole\*:ab,ti

#14. 'isoxazole derivative'/exp

#13. ametopterin:ab,ti OR amethopterin:ab,ti OR abitrexate:ab,ti OR 'a metopterin':ab,ti OR 'a methopterin':ab,ti OR antifolan:ab,ti OR emtexate:ab,ti OR emtrexate:ab,ti OR enthexate:ab,ti OR farmitrexate:ab,ti OR folex:ab,ti OR ledertrexate:ab,ti OR methoblastin:ab,ti OR methohexate:ab,ti OR methotrate:ab,ti OR methylaminopterin:ab,ti OR metotrexat\*:ab,ti OR mtx:ab,ti OR novatrex:ab,ti OR rheumatrex:ab,ti

#12. methotrexate:ab,ti

#11. 'methotrexate'/de

#10. 'disease modifying antirheumatic':ab,ti OR 'disease modifying antirheumatics':ab,ti

#9. dmard\*:ab,ti

#8. antirheumatic\*:ab,ti

#7. 'disease modifying antirheumatic drug'/de

#6. #3 OR #4 OR #5

#5. ((early OR recent\* OR undifferentiated OR persistent OR unclassified) NEAR/3 arthritis):ab,ti

#4. 'rheumatoid arthritis'/exp AND (early:ab,ti OR recent:ab,ti)

#3. #1 AND #2

#2. 'early diagnosis'/de

#1. 'rheumatoid arthritis'/exp

## Coping Strategies

### MEDLINE

1. exp Arthritis, Rheumatoid/

2. exp early diagnosis/

3. 1 and 2

4. exp Arthritis, Rheumatoid/ and (early or recent).tw.

5. ((early or recent\$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.

6. or/3-5

7. exp Adaptation, Psychological/

8. (cope\$ or coping).tw.

9. exp Mind-Body Therapies/

10. (mind adj body).tw.

11. biofeedback.tw.

12. meditat\$.tw.

13. (relaxation adj (therap\$ or technique\$ or training or exercise\$)).tw.

14. (breath\$ adj (technique\$ or exercise\$)).tw.

15. Mindful\$.tw.

16. (mbsr or mbct).tw.

17. (Acceptance-based or (acceptance and commitment)).tw.

18. or/7-17

19. 6 and 18

20. limit 19 to (english language and yr="2005 -Current")

## The Cochrane Library

- #1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
- #2 MeSH descriptor: [Early Diagnosis] explode all trees
- #3 #1 and #2
- #4 (early or recent):ti,ab
- #5 #1 and #4
- #6 ((early or recent\* or undifferentiated or persistent or unclassified) near/3 arthritis):ti,ab
- #7 #3 or #5 or #6
- #8 MeSH descriptor: [Adaptation, Psychological] explode all trees
- #9 (cope\* or coping):ti,ab
- #10 MeSH descriptor: [Mind-Body Therapies] explode all trees
- #11 (mind next body):ti,ab
- #12 biofeedback:ti,ab
- #13 meditat\*:ti,ab
- #14 (relaxation next (therap\* or technique\* or training or exercise\*)):ti,ab
- #15 (breath\* next (technique\* or exercise\*)):ti,ab
- #16 Mindful\*:ti,ab
- #17 (mbsr or mbct):ti,ab
- #18 acceptance-based:ti,ab or (acceptance and commitment):ti,ab
- #19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
- #20 #7 and #19 Publication Year from 2005 to 2015

## EMBASE

- #21. #20 AND ([adolescent]/lim OR [adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py) AND ('article'/it OR 'article in press'/it)
- #20. #19 AND [humans]/lim AND [english]/lim AND [embase]/lim
- #19. #6 AND #18



#18. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#17. 'acceptance based':ab,ti OR (acceptance:ab,ti AND commitment:ab,ti)

#16. mbsr:ab,ti OR mbct:ab,ti

#15. mindful\*:ab,ti

#14. (breath\* NEAR/2 (technique\* OR exercise\*)):ab,ti

#13. (relaxation NEAR/2 (therap\* OR technique\* OR training OR exercise\*)):ab,ti

#12. meditat\*:ab,ti

#11. biofeedback:ab,ti

#10. 'mind body':ab,ti

#9. 'alternative medicine'/exp

#8. cope\*:ab,ti OR coping:ab,ti

#7. 'coping behavior'/exp

#6. #3 OR #4 OR #5

#5. ((early OR recent\* OR undifferentiated OR persistent OR unclassified) NEAR/3 arthritis):ab,ti

#4. 'rheumatoid arthritis'/exp AND (early:ab,ti OR recent:ab,ti)

#3. #1 AND #2

#2. 'early diagnosis'/de

#1. 'rheumatoid arthritis'/exp

## **PsycINFO**

1. rheumatoid arthritis/
2. exp diagnosis/
3. 1 and 2
4. rheumatoid arthritis/ and (early or recent).tw.
5. ((early or recent\$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.
6. or/3-5
7. coping behavior/
8. (cope\$ or coping).tw.
9. mind body therapy/
10. (mind adj body).tw.

11. biofeedback.tw.
12. meditat\$.tw.
13. (relaxation adj (therap\$ or technique\$ or training or exercise\$)).tw.
14. (breath\$ adj (technique\$ or exercise\$)).tw.
15. Mindful\$.tw.
16. (mbsr or mbct).tw.
17. (Acceptance-based or (acceptance and commitment)).tw.
18. or/7-17
19. 6 and 18
20. limit 19 to (english language and yr="2005 -Current")

## Psychological Intervention

### **MEDLINE**

1. exp Arthritis, Rheumatoid/
2. exp early diagnosis/
3. 1 and 2
4. exp Arthritis, Rheumatoid/ and (early or recent).tw.
5. ((early or recent\$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.
6. or/3-5
7. exp Psychotherapy/
8. (psychother\$ or psycholog\$).tw.
9. exp cognitive therapy/
10. (cognitive adj2 therap\$).tw.
11. cbt.tw.
12. (psychoeduc\$ or (psycho adj educ\$)).tw.
13. ((individual or group) adj therap\$).tw.
14. exp Counseling/
15. counsel\$.tw.
16. exp Problem Solving/

17. problem solving.tw.
18. or/7-17
19. 6 and 18
20. limit 19 to (english language and yr="2005 -Current")

### **The Cochrane Library**

- #1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
- #2 MeSH descriptor: [Early Diagnosis] explode all trees
- #3 #1 and #2
- #4 (early or recent):ti,ab
- #5 #1 and #4
- #6 ((early or recent\* or undifferentiated or persistent or unclassified) near/3 arthritis):ti,ab
- #7 #3 or #5 or #6
- #8 MeSH descriptor: [Psychotherapy] explode all trees
- #9 (psychother\* or psychologist\*):ti,ab
- #10 MeSH descriptor: [Cognitive Therapy] explode all trees
- #11 (cognitive near/2 therap\*):ti,ab
- #12 cbt:ti,ab
- #13 (psychoeduc\* or (psycho next educ\*)):ti,ab
- #14 ((individual or group) next therap\*):ti,ab
- #15 MeSH descriptor: [Counseling] explode all trees
- #16 counsel\*:ti,ab
- #17 MeSH descriptor: [Problem Solving] explode all trees
- #18 "problem solving":ti,ab
- #19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
- #20 #7 and #19 Publication Year from 2005 to 2015

### **EMBASE**

#20. #6 AND #18 AND [humans]/lim AND [english]/lim AND [embase]/lim AND ([adolescent]/lim OR [adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py) AND ('article'/it OR 'article in press'/it)

#19. #6 AND #18

#18. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#17. 'problem solving':ab,ti

#16. 'problem solving'/de

#15. counsel\*:ab,ti

#14. 'counseling'/exp

#13. ((individual OR group) NEAR/2 therap\*):ab,ti

#12. psychoeduc\*:ab,ti OR 'psycho education':ab,ti OR 'psycho educational':ab,ti

#11. 'cbt':ab,ti

#10. (cognitive NEAR/2 therap\*):ab,ti

#9. 'cognitive therapy'/exp

#8. psychother\*:ab,ti OR psycholog\*:ab,ti

#7. 'psychotherapy'/exp

#6. #3 OR #4 OR #5

#5. ((early OR recent\* OR undifferentiated OR persistent OR unclassified) NEAR/3 arthritis):ab,ti

#4. 'rheumatoid arthritis'/exp AND (early:ab,ti OR recent:ab,ti)

#3. #1 AND #2

#2. 'early diagnosis'/de

#1. 'rheumatoid arthritis'/exp

## **PsycINFO**

1. rheumatoid arthritis/

2. exp diagnosis/

3. 1 and 2

4. rheumatoid arthritis/ and (early or recent).tw.

5. ((early or recent\$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.

6. or/3-5

7. exp Psychotherapy/
8. (psychother\$ or psycholog\$).tw.
9. cognitive therapy/
10. (cognitive adj2 therap\$).tw.
11. cbt.tw.
12. (psychoeduc\$ or (psycho adj educ\$)).tw.
13. ((individual or group) adj therap\$).tw.
14. exp counseling/
15. counsel\$.tw.
16. exp problem solving/
17. problem solving.tw.
18. or/7-17
19. 6 and 18
20. limit 19 to (english language and yr="2005 -Current")

## Exercises

### **MEDLINE**

1. exp Arthritis, Rheumatoid/
2. exp early diagnosis/
3. 1 and 2
4. exp Arthritis, Rheumatoid/ and (early or recent).tw.
5. ((early or recent\$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.
6. or/3-5
7. exp EXERCISE/
8. Physical Exertion/
9. exp Sports/
10. exp PLIABILITY/
11. exertion\$.tw.

12. exercis\$.tw.
13. sport\$.tw.
14. exp Physical Therapy Modalities/
15. ((physical or motion) adj5 (fitness or therap\$)).tw.
16. (physical\$ adj2 endur\$).tw.
17. manipulat\$.tw.
18. Muscle Strength/
19. ((muscle or strength\$ or extensor or weight) adj (training or resistance)).tw.
20. resistance training.tw.
21. kinesiotherap\$.tw.
22. exp Hydrotherapy/
23. hydrotherap\$.tw.
24. Therapeutic Irrigation.tw.
25. kneipp.tw.
26. exp Balneology/
27. balneo\$.tw.
28. Ammotherap\$.tw.
29. (bath or baths or bathe\$ or bathing).tw.
30. Climatotherapy/
31. climatotherap\$.tw.
32. thalassotherap\$.tw.
33. (water or aqua\$ or climate or mud or spa).tw.
34. or/7-33
35. 6 and 34
36. (animals not (humans and animals)).sh.
37. 35 not 36
38. limit 37 to (english language and yr="2009 -Current")

### **The Cochrane Library**

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees

- #2 MeSH descriptor: [Early Diagnosis] explode all trees
- #3 #1 and #2
- #4 (early or recent):ti,ab
- #5 #1 and #4
- #6 ((early or recent\* or undifferentiated or persistent or unclassified) near/3 arthritis):ti,ab
- #7 #3 or #5 or #6
- #8 MeSH descriptor: [Exercise] explode all trees
- #9 MeSH descriptor: [Physical Exertion] this term only
- #10 MeSH descriptor: [Sports] explode all trees
- #11 MeSH descriptor: [Pliability] explode all trees
- #12 exertion\*:ti,ab
- #13 exercis\*:ti,ab
- #14 sport\*:ti,ab
- #15 MeSH descriptor: [Physical Therapy Modalities] explode all trees
- #16 ((physical or motion) near/5 (fitness or therap\*)):ti,ab
- #17 (physical\* near/2 endur\*):ti,ab
- #18 manipul\*:ti,ab
- #19 MeSH descriptor: [Muscle Strength] this term only
- #20 ((muscle or strength\* or extensor or weight) next (training or resistance)):ti,ab
- #21 "resistance training":ti,ab
- #22 kinesiotherap\*:ti,ab
- #23 MeSH descriptor: [Hydrotherapy] explode all trees
- #24 hydrotherap\*:ti,ab
- #25 "Therapeutic Irrigation":ti,ab
- #26 kneipp:ti,ab
- #27 MeSH descriptor: [Balneology] explode all trees
- #28 balneo\*:ti,ab
- #29 Ammotherap\*:ti,ab
- #30 (bath or baths or bathe\$ or bathing):ti,ab
- #31 MeSH descriptor: [Climatotherapy] this term only
- #32 climatotherap\*:ti,ab

- #33 thalassotherap\*:ti,ab
- #34 (water or aqua\* or climate or mud or spa):ti,ab
- #35 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
- #36 #7 and #35 Publication Year from 2009 to 2015

## EMBASE

#37. #6 AND #35 AND [humans]/lim AND [english]/lim AND [embase]/lim AND AND (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py) AND ('article'/it OR 'article in press'/it)

#36. #6 AND #35

#35. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #30 OR #31 OR #32 OR #33 OR #34

#34. water:ab,ti OR aqua\*:ab,ti OR climate:ab,ti OR mud:ab,ti OR spa:ab,ti

#33. thalassotherap\*:ab,ti

#32. climatotherap\*:ab,ti

#31. 'climatotherapy'/de

#30. bath:ab,ti OR baths:ab,ti OR bathe\*:ab,ti OR bathing:ab,ti

#28. ammotherap\*:ab,ti

#27. balneo\*:ab,ti

#26. 'balneotherapy'/exp

#25. kneipp:ab,ti

#24. 'therapeutic irrigation':ab,ti

#23. hydrotherap\*:ab,ti

#22. 'hydrotherapy'/de

#21. kinesiotherap\*:ab,ti

#20. 'kinesiotherapy'/exp

#19. 'resistance training':ab,ti

#18. muscle:ab,ti OR strength\*:ab,ti OR extensor:ab,ti OR weight:ab,ti AND next:ab,ti AND (training:ab,ti OR resistance:ab,ti)

#17. 'muscle strength'/de



- #16. manipul\*:ab,ti
- #15. (physical\* NEAR/2 endur\*):ab,ti
- #14. ((physical OR motion) NEAR/5 (fitness OR therap\*)):ab,ti
- #13. 'physiotherapy'/exp
- #12. sport\*:ab,ti
- #11. exercis\*:ab,ti
- #10. exertion\*:ab,ti
- #9. 'pliability'/de
- #8. 'sport'/exp
- #7. 'exercise'/exp
- #6. #3 OR #4 OR #5
- #5. ((early OR recent\* OR undifferentiated OR persistent OR unclassified) NEAR/3 arthritis):ab,ti
- #4. 'rheumatoid arthritis'/exp AND (early:ab,ti OR recent:ab,ti)
- #3. #1 AND #2
- #2. 'early diagnosis'/de
- #1. 'rheumatoid arthritis'/exp

Smoking cessation

## **MEDLINE**

- 1. exp Arthritis, Rheumatoid/
- 2. exp early diagnosis/
- 3. 1 and 2
- 4. exp Arthritis, Rheumatoid/ and (early or recent).tw.
- 5. ((early or recent\$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.
- 6. or/3-5
- 7. exp "Tobacco Use Cessation"/
- 8. ((tobacco or cigarette\$ or smoke\$ or smoking or nicotine) and (quit\$ or cease\$ or cessation or stop\$)).tw.
- 9. 7 or 8

10. 6 and 9

### The Cochrane Library

- #1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
- #2 MeSH descriptor: [Early Diagnosis] explode all trees
- #3 #1 and #2
- #4 (early or recent):ti,ab
- #5 #1 and #4
- #6 ((early or recent\* or undifferentiated or persistent or unclassified) near/3 arthritis):ti,ab
- #7 #3 or #5 or #6
- #8 MeSH descriptor: [Tobacco Use Cessation] explode all trees
- #9 ((tobacco or cigarette\* or smoke\* or smoking or nicotine) and (quit\* or cease\* or cessation or stop\*)):ti,ab
- #10 #8 OR #9
- #11 #7 AND #10

### EMBASE

- #12. #11 AND [humans]/lim AND [english]/lim AND [embase]/lim AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py) AND 'article'/it
- #11. #6 AND #10
- #10. #7 OR #8 OR #9
- #9. ((tobacco or cigarette\* or smoke\* or smoking or nicotine) and (quit\* or cease\* or cessation or stop\*)):ab,ti
- #8. 'smoking cessation program'/de
- #7. 'smoking cessation'/de
- #6. #3 OR #4 OR #5
- #5. ((early OR recent\* OR undifferentiated OR persistent OR unclassified) NEAR/3 arthritis):ab,ti
- #4. 'rheumatoid arthritis'/exp AND (early:ab,ti OR recent:ab,ti)
- #3. #1 AND #2

#2. 'early diagnosis'/de

#1. 'rheumatoid arthritis'/exp

## II. NSAIDs

### MEDLINE

1. exp Arthritis, Rheumatoid/
2. exp early diagnosis/
3. 1 and 2
4. exp Arthritis, Rheumatoid/ and (early or recent).tw.
5. ((early or recent\$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.
6. or/3-5
7. exp Anti-Inflammatory Agents, Non-Steroidal/
8. (Anti-Inflammator\$ or AntiInflammator\$).tw.
9. (Anti adj Inflammator\$).tw.
10. (nonsteroid\$ or non-steroid\$).tw.
11. (non adj steroid\$).tw.
12. nsaid\$.tw.
13. Ampyrone.tw.
14. Antipyrine.tw.
15. Apazone.tw.
16. Aspirin.tw.
17. Bufexamac.tw.
18. Clofazimine.tw.
19. Clonixin.tw.
20. Curcumin.tw.
21. Diclofenac.tw.
22. Diflunisal.tw.
23. Dipyrrone.tw.

24. Epirizole.tw.
25. Etodolac.tw.
26. Fenoprofen.tw.
27. Flurbiprofen.tw.
28. Ibuprofen.tw.
29. Indomethacin.tw.
30. Ketoprofen.tw.
31. Ketorolac.tw.
32. Meclofenamic Acid.tw.
33. Mefenamic Acid.tw.
34. Mesalamine.tw.
35. Naproxen.tw.
36. Niflumic Acid.tw.
37. Oxyphenbutazone.tw.
38. Phenylbutazone.tw.
39. Piroxicam.tw.
40. Prenazone.tw.
41. Salicylate\$.tw.
42. Sulfasalazine.tw.
43. Sulindac.tw.
44. Suprofen.tw.
45. Tolmetin.tw.
46. or/7-45
47. 6 and 46
48. randomized controlled trial.pt.
49. controlled clinical trial.pt.
50. randomized.ab.
51. placebo.ab.
52. drug therapy.fs.
53. randomly.ab.
54. trial.ab.

- 55. groups.ab.
- 56. or/48-55
- 57. (animals not (humans and animals)).sh.
- 58. 56 not 57
- 59. 47 and 58
- 60. limit 59 to "all adult (19 plus years)"
- 61. limit 60 to yr="2005 -Current"
- 62. limit 61 to english language

### **The Cochrane Library**

- #1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
- #2 MeSH descriptor: [Early Diagnosis] explode all trees
- #3 #1 and #2
- #4 (early or recent):ti,ab
- #5 #1 and #4
- #6 ((early or recent\* or undifferentiated or persistent or unclassified) near/3 arthritis):ti,ab
- #7 #3 or #5 or #6
- #8 MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
- #9 Anti-Inflamator\*:ti,ab or (Anti next Inflammator\*):ti,ab or AntiInflamator\*:ti,ab
- #10 (nonsteroid\* or non-steroid\*):ti,ab or (non next steroid\*):ti,ab
- #11 nsaid\*:ti,ab
- #12 Ampyrone:ti,ab
- #13 Antipyrine:ti,ab
- #14 Apazone:ti,ab
- #15 Aspirin:ti,ab
- #16 Bufexamac:ti,ab
- #17 Clofazimine:ti,ab
- #18 Clonixin:ti,ab
- #19 Curcumin:ti,ab
- #20 Diclofenac:ti,ab
- #21 Diflunisal:ti,ab

- #22 Dipyrrone:ti,ab
- #23 Epirizole:ti,ab
- #24 Etodolac:ti,ab
- #25 Fenoprofen:ti,ab
- #26 Flurbiprofen:ti,ab
- #27 Ibuprofen:ti,ab
- #28 Indomethacin:ti,ab
- #29 Ketoprofen:ti,ab
- #30 Ketorolac:ti,ab
- #31 "Meclofenamic Acid":ti,ab
- #32 "Mefenamic Acid":ti,ab
- #33 Mesalamine:ti,ab
- #34 Naproxen:ti,ab
- #35 "Niflumic Acid":ti,ab
- #36 Oxyphenbutazone:ti,ab
- #37 Phenylbutazone:ti,ab
- #38 Piroxicam:ti,ab
- #39 Prenazone:ti,ab
- #40 Salicylate\*:ti,ab
- #41 Sulfasalazine:ti,ab
- #42 Sulindac:ti,ab
- #43 Suprofen:ti,ab
- #44 Tolmetin:ti,ab
- #45 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44
- #46 #7 and #45 Publication Year from 2005 to 2015

## EMBASE

#52. #51 AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py) AND ('article'/it OR 'article in press'/it)

#51. #45 AND #49 AND [humans]/lim AND [english]/lim AND [embase]/lim

#50. #45 AND #49

#49. #46 OR #47 OR #48

#48. 'health care quality'/exp

#47. clinical AND trial\*

#46. random\*:ab,ti

#45. #6 AND #44

#44. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19  
OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32  
OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43

#43. tolmetin:ab,ti

#42. suprofen:ab,ti

#41. sulindac:ab,ti

#40. sulfasalazine:ab,ti

#39. salicylate\*:ab,ti

#38. pnenazone:ab,ti

#37. piroxicam:ab,ti

#36. phenylbutazone:ab,ti

#35. oxyphenbutazone:ab,ti

#34. 'niflumic acid':ab,ti

#33. naproxen:ab,ti

#32. mesalamine:ab,ti

#31. 'meclofenamic acid':ab,ti

#30. 'meclofenamic acid':ab,ti

#29. ketoprofen:ab,ti

#28. ketoprofen:ab,ti

#27. indomethacin:ab,ti

#26. ibuprofen:ab,ti

#25. fenoprofen:ab,ti

#24. etodolac:ab,ti

#23. eprizole:ab,ti

#22. dipyrrone:ab,ti

- #21. diflunisal:ab,ti
- #20. diclofenac:ab,ti
- #19. curcumin:ab,ti
- #18. clonixin:ab,ti
- #17. clofazimine:ab,ti
- #16. bufexamac:ab,ti
- #15. aspirin:ab,ti
- #14. apazone:ab,ti
- #13. antipyrine:ab,ti
- #12. ampyrone:ab,ti
- #11. nsaid\*:ab,ti
- #10. nonsteroid\*:ab,ti OR 'non steroid':ab,ti OR 'non steroidal':ab,ti
- #9. 'anti inflammatory':ab,ti OR 'anti inflammatories':ab,ti
- #8. antiinflammator\*:ab,ti
- #7. 'nonsteroid antiinflammatory agent'/exp
- #6. #3 OR #4 OR #5
- #5. ((early OR recent\* OR undifferentiated OR persistent OR unclassified) NEAR/3 arthritis):ab,ti
- #4. 'rheumatoid arthritis'/exp AND (early:ab,ti OR recent:ab,ti)
- #3. #1 AND #2
- #2. 'early diagnosis'/de
- #1. 'rheumatoid arthritis'/exp

### **III. GLUCOCORTICOIDS (GC)**

#### **MEDLINE**

- 1. exp Arthritis, Rheumatoid/
- 2. exp early diagnosis/
- 3. 1 and 2
- 4. exp Arthritis, Rheumatoid/ and (early or recent).tw.
- 5. ((early or recent\$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.



6. or/3-5
7. exp steroids/
8. (steroid\$ or corticosteroid\$).tw.
9. Adrenocorticotrophic Hormone/
10. exp Adrenal Cortex Hormones/
11. Glucocorticoid\$.tw.
12. predniso\$.tw.
13. Flupredni\$.tw.
14. fluocinonide.tw.
15. Prednimustine.tw.
16. betamet?asone.tw.
17. triamcinolone.tw.
18. cortivazol.af.
19. cortison\$.tw.
20. beclometas\$.tw.
21. hydrocort\$.tw.
22. parametas\$.tw.
23. dexamet\$.tw.
24. methylpred\$.tw.
25. fluocortolone.tw.
26. corticotropin.tw.
27. budesonide.tw.
28. desonide.tw.
29. or/7-28
30. 6 and 29
31. randomized controlled trial.pt.
32. controlled clinical trial.pt.
33. randomized.ab.
34. placebo.ab.
35. drug therapy.fs.
36. randomly.ab.

- 37. trial.ab.
- 38. groups.ab.
- 39. or/31-38
- 40. exp animals/ not humans.sh.
- 41. 39 not 40
- 42. 30 and 41
- 43. limit 42 to "all adult (19 plus years)"
- 44. limit 43 to (english language and yr="2013 -Current")

### **The Cochrane Library**

- #1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
- #2 MeSH descriptor: [Early Diagnosis] explode all trees
- #3 #1 and #2
- #4 (early or recent):ti,ab
- #5 #1 and #4
- #6 ((early or recent\* or undifferentiated or persistent or unclassified) near/3 arthritis):ti,ab
- #7 #3 or #5 or #6
- #8 MeSH descriptor: [Steroids] explode all trees
- #9 (steroid\* or corticosteroid\*):ti,ab
- #10 MeSH descriptor: [Adrenocorticotrophic Hormone] this term only
- #11 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
- #12 Glucocorticoid\*:ti,ab
- #13 predniso\*:ti,ab
- #14 Flupredni\*:ti,ab
- #15 fluocinonide:ti,ab
- #16 Prednimustine:ti,ab
- #17 betamet?asone:ti,ab
- #18 triamcinolone:ti,ab
- #19 cortivazol
- #20 cortison\*:ti,ab
- #21 beclometas\*:ti,ab

- #22 hydrocort\*:ti,ab
- #23 parametas\*:ti,ab
- #24 dexamet\*:ti,ab
- #25 methylpred\*:ti,ab
- #26 fluocortolone:ti,ab
- #27 corticotropin:ti,ab
- #28 budesonide:ti,ab
- #29 desonide:ti,ab
- #30 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
- #31 #7 and #30 Publication Year from 2013 to 2015

#### **EMBASE**

- #36. #35 AND [humans]/lim AND [english]/lim AND [embase]/lim AND (2013:py OR 2014:py OR 2015:py) AND ('article'/it OR 'article in press'/it)
- #35. #6 AND #30 AND #34
- #34. #31 OR #32 OR #33
- #33. 'health care quality'/exp
- #32. clinical AND trial\*
- #31. random\*:ab,ti
- #30. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
- #29. desonide:ab,ti
- #28. desonide:ab,ti
- #27. budesonide:ab,ti
- #26. corticotropin:ab,ti
- #25. fluocortolone:ab,ti
- #24. methylpred\*:ab,ti
- #23. dexamet\*:ab,ti
- #22. parametas\*:ab,ti
- #21. hydrocort\*:ab,ti
- #20. beclometas\*:ab,ti

- #19. 'cortivazol'
- #18. cortison\*:ab,ti
- #17. 'cortivazol'
- #16. triamcinolone:ab,ti
- #15. betametasone:ab,ti OR betamethasone:ab,ti
- #14. prednimustine:ab,ti
- #13. fluocinonide:ab,ti
- #12. flupredni\*:ab,ti
- #11. predniso\*:ab,ti
- #10. glucocorticoid\*:ab,ti
- #9. 'glucocorticoid'/exp
- #8. steroid\*:ab,ti OR corticosteroid\*:ab,ti
- #7. 'steroid'/exp
- #6. #3 OR #4 OR #5
- #5. ((early OR recent\* OR undifferentiated OR persistent OR unclassified) NEAR/3 arthritis):ab,ti
- #4. 'rheumatoid arthritis'/exp AND (early:ab,ti OR recent:ab,ti)
- #3. #1 AND #2
- #2. 'early diagnosis'/de
- #1. 'rheumatoid arthritis'/exp

#### **IV. DMARDs**

##### **MEDLINE**

- 1. exp Arthritis, Rheumatoid/
- 2. exp early diagnosis/
- 3. 1 and 2
- 4. exp Arthritis, Rheumatoid/ and (early or recent).tw.
- 5. ((early or recent\$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.
- 6. or/3-5
- 7. Antirheumatic Agents/

8. Antirheumatic\$.tw.
9. dmard\$.tw.
10. disease modifying antirheumatic\$.tw.
11. Methotrexate/
12. Methotrexate.tw.
13. (Abitrexate or amet?opterine or Abitrexate or A Met?opterine\$ or Antifolan or Emt?exate or Enthexate or Farmitrexate or Folex or Ledertrexate or Methoblastin or Methohexate or Methotrate or Methylaminopterin or Metotrexat\$ or mtx or Novatrex or Rheumatrex).tw.
14. exp Isoxazoles/
15. isoxazole\$.tw.
16. leflunomide\$.tw.
17. (Afiancen or Arabloc or Arava or Artrilab or Artrimod or Filartros or Inmunoartro or Lefluar or Leflucross or Lefno or Lefra or Lefumide or Lisifen or Molagar or Repso or Rumalef).tw.
18. Sulfasalazine/
19. sulfasalazine.tw.
20. (Salazosulfapyridine or sulfasalazine or Sulfosalazine or Sulfasal#zine or Salazopyridin\$ or asulfidine or azulf#dine).tw.
21. Hydroxychloroquine/
22. Hydroxychloro\$.tw.
23. (Axokineor or Dolquine or Ercoquin or Evoquin or HCQS or HQT or Hydrocad or Hydroquin or Ilinol or Immard or Metirel or Narbon or Oxcq or Oxiklorin or Oxy-Q or Plaquen?l or Polirreuminor or Quensyl or Reuquinol).tw.
24. exp Gold Compounds/
25. exp Organogold Compounds/
26. gold.tw.
27. exp Chloroquine/
28. chloroquine\$.tw.
29. (aralen or arechine or arequin or chingamin or chlorochin or khingamin or nivaquine or oxychloroquine or oxychlorochin or plaquinol or plaquinil or quensy or anoclor or arthrabas or avlocor or cidanchin or clopirim or collagenan or daraclor or daramal or dichinalex or difosquin or diroquine or genocin or heliopar or klorokin or malarex or malaviron or mirquin or nivaquine or novo-chloroquine or novochloroquine or paluken or palux or pharmaquinine or plasmquine or promal or p-roquine or resoquin\$ or savarine or syncoquin or weimerquin).tw.
30. Azathioprine/
31. azathioprine.tw.

32. (Aseroprim or Aseroprin or Azaallen or Azadus or Azafalk or Azafor or Azafrine or Azaglux or Azahexal or Aza?mun\$ or Azamedac or Azap or Azap?in\$ or Azapress or Aza-Q or Azarek or Azasan or Azathiodura or Azathiodura or Azathioregio or Azatrimem or Azimune or Azop?in\$ or Azoran or Berkaprine or Colinsan or Glaxoprin or Immunoprin or Imuger or Imunen or Imuprin\$ or Imuran or Imure?or Imuzat or Oprisine or Satedon or Thioprine or Tiosalprin or Transimune or Zaprine or Zytrim).tw.

33. exp Cyclosporins/

34. c?closporin\$.tw.

35. (neoral or gengraf or restasis or sandimmun\$ or sangcya).tw.

36. exp Penicillamine/

37. Penicillamine.tw.

38. (Adalkenor or Artamin or Atamir or Byanodine or Cilamin or Cuprenil or Cuprimine or Cupripen or Depen or Distamin\$ or D-Penamine or Gerodyl or Kelatin\$ or Mercaptyl or Metalcaptase or Pendramine or Rhumantin or Sufortan\$ or Trisorcin or Trolovol).tw.

39. exp Cyclophosphamide/

40. (cyclophosph\$ or cytophosphan or Cytoxan or sendoxan or endoxan or neosar or nsc-26271 or procytox or b-518 or ifosfamide or isophosphamide or iphosphamide or isofosfamide or holoxan or nsc-109\$ or asta z 4942 or cfx or phosphoramide mustard\$.tw.

41. Mycophenolic Acid/

42. mycophenolate.tw.

43. (Arzip or Baxmune or CellCept or Cellmune or Celprot or Ceptolate or Imulate or Imuxgen or Lanfetil or Limfocept or Metocris or Micocept or MMF or Mofecept or Mofetyl or Mofilel or Mofimutral or Mometil or Mophecen or Munotras or Myaccord or Mycept or Myclausenor or Mycofenor or Mycolat or Mycoldosa or Mycophen or Myfenax Myfetil or Mygref or Myotec or Mysept or Presumin or Refrat or Renocell or Supresta or Tevacept or Trixin).tw.

44. exp Chlorambucil/

45. chlorambucil.tw.

46. (Amboclorin or Clokeran or Leukeran or Linfoctin or Lympholysin).tw.

47. Minocycline/

48. minocyclin\$.tw.

49. (Acneclin or Akamin or Aknemin or Akne-Puren or Aknereduct or Aknin-Mino or Aknin-N or Aknoral or Aknosan or Apominolin or Arestinor or Auramin or Blemix or Borymycin or Cipancin or Cyclimycin or Dentomycin\$ or durakne or Dynacin or Enca or Icht-Oralor or Klinoc or Klinomycin or Klinotab or Lederderm or Logryx or Meibi or Mestacine or Micromycin or Minac 50 or Minakne or Minaxen or Mino-50 or Minocin or Minoclin or Minodene or Minoderm or Minogalen or Minolis or Minomax or Minomycin or Minoplus or Minosil or Minostad or Minotab\$ or Minotekor or Minotrex or Minotyrol or Mino-Wolff or Minox or Mynocine or Myrac or Oracyclin or Parocline or Periodiline or Peritrol or Ranmino or Romin or Seboclear or Sebomin or Sebren or Skid or Skinocyclin or Solodyn or Spicline or Triomin or Udimin or Vectrin or Yelnac or Zacnan).tw.

- 50. Pyrroles/
- 51. tofacitinib.tw.
- 52. Xeljanz.tw.
- 53. baricitinib.tw.
- 54. or/7-52
- 55. 6 and 54
- 56. (animals not (humans and animals)).sh.
- 57. 55 not 56
- 58. limit 57 to "all adult (19 plus years)"
- 59. limit 58 to (english language and yr="2005 -Current")

### **The Cochrane Library**

- #1 MeSH descriptor: [Antirheumatic Agents] explode all trees
- #2 Antirheumatic\*:ti,ab
- #3 dmard\*:ti,ab
- #4 "disease modifying antirheumatic\*":ti,ab
- #5 MeSH descriptor: [Methotrexate] this term only
- #6 Methotrexate:ti,ab
- #7 (Abitrexate or amet?opterine or Abitrexate or A Met?opterine\* or Antifolan or Emt?exate or Enthexate or Farnitrexate or Folex or Ledertrexate or Methoblastin or Methohexate or Methotrate or Methylaminopterin or Metotrexat\$ or mtx or Novatrex or Rheumatrex):ti,ab
- #8 MeSH descriptor: [Isoxazoles] explode all trees
- #9 isoxazole\*:ti,ab
- #10 leflunomide\*:ti,ab
- #11 (Afiancen or Arabloc or Arava or Artrilab or Artrimod or Filartros or Inmunoartro or Lefluar or Leflucross or Lefno or Lefra or Lefumide or Lisifen or Molagar or Repso or Rumalef):ti,ab
- #12 MeSH descriptor: [Sulfasalazine] this term only
- #13 sulfasalazine:ti,ab
- #14 (Salazosulfapyridine or sulfasalazine or Sulfosalazine or Sulfasal?zine or Salazopyridin\* or asulfidine or azulf?dine):ti,ab
- #15 MeSH descriptor: [Hydroxychloroquine] this term only
- #16 Hydroxychloro\*:ti,ab

- #17 (Axokineor or Dolquine or Ercoquin or Evoquin or HCQS or HQT or Hydrocad or Hydroquin or Ilinol or Immard or Metirel or Narbon or Oxcq or Oxiklorin or Oxy-Q or Plaquen?l or Polirreuminor or Quensyl or Reuquinol):ti,ab
- #18 MeSH descriptor: [Gold Compounds] explode all trees
- #19 MeSH descriptor: [Organogold Compounds] explode all trees
- #20 gold:ti,ab
- #21 MeSH descriptor: [Chloroquine] explode all trees
- #22 chloroquine\*:ti,ab
- #23 (aralen or arechine or arequin or chingamin or chlorochin or khingamin or nivaquine or oxychloroquine or oxychlorochin or plaquinol or plaquinil or quensy or anoclor or arthrabas or avloclor or cidanchin or clopirim or collagenan or daraclor or daramal or dichinalex or difosquin or diroquine or genocin or heliopar or klorokin or malarex or malaviron or mirquin or nivaquine or novo-chloroquine or novochloroquine or paluken or palux or pharmaquinine or plasmquine or promal or p-roquine or resoquin\$ or savarine or syncoquin or weimerquin):ti,ab
- #24 MeSH descriptor: [Azathioprine] this term only
- #25 azathioprine:ti,ab
- #26 (Aseroprim or Aseroprin or Azaallen or Azadus or Azafalk or Azafor or Azafrine or Azag lax or Azahexal or Aza?mun\* or Azamedac or Azap or Azap?in\* or Azapress or Aza-Q or Azarek or Azasan or Azathiodura or Azathiodura or Azathioregio or Azatrilem or Azimune or Azop?in\* or Azoran or Berkaprime or Colinsan or Glaxoprin or Immunoprin or Imuger or Imunen or Imuprin\$ or Imuran or Imure? or Imuzat or Oprisine or Satedon or Thioprine or Tiosalprin or Transimune or Zaprine or Zytrim):ti,ab
- #27 MeSH descriptor: [Cyclosporins] explode all trees
- #28 c?closporin\*:ti,ab
- #29 (neoral or gengraf or restasis or sandimmun\* or sangcya):ti,ab
- #30 MeSH descriptor: [Penicillamine] explode all trees
- #31 Penicillamine:ti,ab
- #32 (Adalkenor or Artamin or Atamir or Byanodine or Cilamin or Cuprenil or Cuprimine or Cupripen or Depen or Distamin\* or D-Penammine or Gerodyl or Kelatin\* or Mercaptyl or Metalcaptase or Pendramine or Rhumantim or Sufortan\* or Trisorcin or Trolovol):ti,ab
- #33 MeSH descriptor: [Cyclophosphamide] explode all trees
- #34 (cyclophosph\* or cytophosphan or Cytoxan or sendoxan or endoxan or neosar or nsc-26271 or procytox or b-518 or ifosfamidine or isophosphamide or iphosphamide or isofosfamidine or holoxan or nsc-109\* or "asta z 4942" or cfx or "phosphoramidine mustard\*"):ti,ab
- #35 MeSH descriptor: [Mycophenolic Acid] this term only
- #36 mycophenolate:ti,ab



- #37 (Arzip or Baxmune or CellCept or Cellmune or Celprot or Ceptolate or Imulate or muxgen or Lanfetil or Limfocept or Metocris or Micocept or MMF or Mofecept or Mofetyl or Mofilel or Mofimutral or Mometil or Mophecen or Munotras or Myaccord or Mycept or Myclausenor or Mycofenor or Mycolat or Mycoldosa or Mycophen or Myfenax Myfetil or Mygref or Myotec or Mysept or Presumin or Refrat or Renocell or Supresta or Tevacept or Trixin):ti,ab
- #38 MeSH descriptor: [Chlorambucil] explode all trees
- #39 chlorambucil:ti,ab
- #40 (Amboclorin or Clokeran or Leukeran or Linfoylisin or Lympholysin):ti,ab
- #41 MeSH descriptor: [Minocycline] this term only
- #42 minocyclin\*:ti,ab
- #43 (Acneclin or Akamin or Aknemin or Akne-Puren or Aknereduct or Akinin-Mino or Akinin-N or Aknoral or Aknosan or Apominolin or Arestinor or Auramin or Blemix or Borymycin or Cipancin or Cyclimycin or Dentomyacin\* or durakne or Dynacin or Enca or Icht-Oralor or Klinoc or Klinomycin or Klinotab or Lederderm or Logryx or Meibi or Mestacine or Micromycin or "Minac 50" or Minakne or Minaxen or Mino-50 or Minocin or Minoclin or Minodene or Minoderma or Minogalen or Minolis or Minomax or Minomycin or Minoplus or Minosil or Minostad or Minotab\* or Minotekor or Minotrex or Minotyrol or Mino-Wolff or Minox or Mynocine or Myrac or Oracyclin or Parocline or Periocline or Peritrol or Ranmino or Romin or Seboclear or Sebomin or Sebren or Skid or Skinocyclin or Solodyn or Spicline or Triomin or Udimin or Vectrin or Yelnac or Zacnan):ti,ab
- #44 MeSH descriptor: [Pyrroles] this term only
- #45 tofacitinib:ti,ab
- #46 Xeljanz:ti,ab
- #47 baricitinib:ti,ab
- #48 #1 or #2 or #3 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 OR #47
- #49 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
- #50 MeSH descriptor: [Early Diagnosis] explode all trees
- #51 #48 and #49
- #52 (early or recent):ti,ab
- #53 #48 and #51
- #54 ((early or recent\* or undifferentiated or persistent or unclassified) near/3 arthritis):ti,ab
- #55 #51 or #53 or #54
- #56 #48 and #55 Publication Year from 2005 to 2015

## EMBASE

#52. #51 AND [humans]/lim AND [english]/lim AND [embase]/lim AND AND ([adolescent]/lim OR [adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py) AND ('Article'/it OR 'Article in Press'/it)

#51. #6 AND #50

#50. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49

#49. Baricitinib:ab,ti

#48. xeljanz:ab,ti

#47. tofacitinib:ab,ti

#46. acneclin:ab,ti OR akamin:ab,ti OR aknemin:ab,ti OR 'akne puren':ab,ti OR aknereduct:ab,ti OR 'aknin mino':ab,ti OR 'aknin n':ab,ti OR aknoral:ab,ti OR aknosan:ab,ti OR apominolin:ab,ti OR arestinor:ab,ti OR auramin:ab,ti OR blemix:ab,ti OR borymycin:ab,ti OR cipancin:ab,ti OR cyclimycin:ab,ti OR dentomycin\*:ab,ti OR durakne:ab,ti OR dynacin:ab,ti OR enca:ab,ti OR 'icht oralor':ab,ti OR klinoc:ab,ti OR klinomycin:ab,ti OR klinotab:ab,ti OR lederderm:ab,ti OR logryx:ab,ti OR meibi:ab,ti OR mestacine:ab,ti OR micromycin:ab,ti OR 'minac 50':ab,ti OR minakne:ab,ti OR minaxen:ab,ti OR 'mino 50':ab,ti OR minocin:ab,ti OR minoclin:ab,ti OR minodene:ab,ti OR minoderm:ab,ti OR minogalen:ab,ti OR minolis:ab,ti OR minomax:ab,ti OR minomycin:ab,ti OR minoplus:ab,ti OR minosil:ab,ti OR minostad:ab,ti OR minotab\*:ab,ti OR minotekor:ab,ti OR minotrex:ab,ti OR minotyrol:ab,ti OR 'mino wolff':ab,ti OR minox:ab,ti OR mynocine:ab,ti OR myrac:ab,ti OR oracyclin:ab,ti OR parocline:ab,ti OR periocline:ab,ti OR peritrol:ab,ti OR ranmino:ab,ti OR romin:ab,ti OR seboclear:ab,ti OR sebomin:ab,ti OR sebren:ab,ti OR skid:ab,ti OR skinocyclin:ab,ti OR solodyn:ab,ti OR spicline:ab,ti OR triomin:ab,ti OR udimin:ab,ti OR vectrin:ab,ti OR yelnac:ab,ti OR zacnan:ab,ti

#45. minocyclin\*:ab,ti

#44. 'minocycline'/de

#43. amboclorin:ab,ti OR clokeran:ab,ti OR leukeran:ab,ti OR linfolysin:ab,ti OR lympholysin:ab,ti

#42. chlorambucil:ab,ti

#41. 'chlorambucil'/de

#40. arzip:ab,ti OR baxmune:ab,ti OR cellcept:ab,ti OR cellmune:ab,ti OR celprot:ab,ti OR

ceptolate:ab,ti OR imulate:ab,ti OR muxgen:ab,ti OR lanfetil:ab,ti OR limfocept:ab,ti OR

metocris:ab,ti OR micocept:ab,ti OR mmf:ab,ti OR mofecept:ab,ti OR mofetyl:ab,ti OR mofilelet:ab,ti OR mofimutral:ab,ti OR mometil:ab,ti OR mophecen:ab,ti OR munotras:ab,ti OR myaccord:ab,ti OR mycept:ab,ti OR myclausenor:ab,ti OR mycofenor:ab,ti OR mycolat:ab,ti OR mycoldosa:ab,ti OR mycophen:ab,ti OR myfenax:ab,ti AND myfetil:ab,ti

OR mygref:ab,ti OR myotec:ab,ti OR mysept:ab,ti OR presumin:ab,ti OR refrat:ab,ti OR

renocell:ab,ti OR supresta:ab,ti OR tevacept:ab,ti OR trixin:ab,ti

#39. mycophenolate:ab,ti

#38. 'mycophenolic acid'/de

#37. cyclophosph\*:ab,ti OR cytophosphan:ab,ti OR cytoxan:ab,ti OR sendoxan:ab,ti OR endoxan:ab,ti  
OR neosar:ab,ti OR 'nsc 26271':ab,ti OR procytox:ab,ti OR 'b 518':ab,ti OR  
ifosfamide:ab,ti OR isophosphamide:ab,ti OR iphosphamide:ab,ti OR isofosfamide:ab,ti OR  
holoxan:ab,ti OR 'nsc 109':ab,ti OR 'asta z 4942':ab,ti OR cfx:ab,ti OR 'phosphoramidate  
mustard':ab,ti OR 'phosphoramidate mustards':ab,ti

#36. 'cyclophosphamide'/de

#35. adalcanor:ab,ti OR artamin:ab,ti OR atamir:ab,ti OR byanodine:ab,ti OR cilamin:ab,ti OR  
cuprenil:ab,ti OR cuprimine:ab,ti OR cupripen:ab,ti OR depen:ab,ti OR distamin\*:ab,ti  
OR 'd penamine':ab,ti OR gerodyl:ab,ti OR kelatin\*:ab,ti OR mercaptyl:ab,ti OR  
metalcaptase:ab,ti OR pendramine:ab,ti OR rhumantim:ab,ti OR sufortan\*:ab,ti OR trisorcin:ab,ti  
OR trolovol:ab,ti

#34. 'penicillamine'/de

#33. neoral:ab,ti OR gengraf:ab,ti OR restasis:ab,ti OR sandimmun\*:ab,ti OR sangcya:ab,ti

#32. cyclosporin\*:ab,ti OR ciclosporin\*:ab,ti

#31. 'cyclosporin derivative'/de

#30. aseroprim:ab,ti OR aseroprin:ab,ti OR azaallen:ab,ti OR azadus:ab,ti OR azafalk:ab,ti  
OR azafor:ab,ti OR azafrine:ab,ti OR azaglaax:ab,ti OR azahexal:ab,ti OR azamun\*:ab,ti  
OR azaimun:ab,ti OR azamedac:ab,ti OR azap:ab,ti OR azapin\*:ab,ti OR azaprine\*:ab,ti OR  
azapress:ab,ti OR 'aza q':ab,ti OR azarek:ab,ti OR azasan:ab,ti OR azathiodura:ab,ti OR  
azathioregio:ab,ti OR azatrimem:ab,ti OR azimune:ab,ti OR azopin\*:ab,ti OR azoran:ab,ti OR  
berkaprine:ab,ti OR colinsan:ab,ti OR glaxoprin:ab,ti OR immunoprin:ab,ti OR imuger:ab,ti OR  
imunen:ab,ti OR imuprin\*:ab,ti OR imuran:ab,ti OR imure\*:ab,ti OR imuzat:ab,ti OR  
oprisine:ab,ti OR satedon:ab,ti OR thioprine:ab,ti OR tiosalprin:ab,ti OR transimune:ab,ti OR  
zaprine:ab,ti OR zytrim:ab,ti

#29. azathioprine:ab,ti

#28. 'azathioprine'/de

#27. aralen:ab,ti OR arechine:ab,ti OR arequin:ab,ti OR chingamin:ab,ti OR chlorochin:ab,ti OR  
khangamin:ab,ti OR oxychloroquine:ab,ti OR oxychlorochin:ab,ti OR plaquinol:ab,ti OR  
plaquinil:ab,ti OR quensy:ab,ti OR anoclor:ab,ti OR arthrabas:ab,ti OR avloclor:ab,ti OR  
cidanchin:ab,ti OR clopirim:ab,ti OR collagenan:ab,ti OR daraclor:ab,ti OR daramal:ab,ti OR  
dichinalax:ab,ti OR difosquin:ab,ti OR diroquine:ab,ti OR genocin:ab,ti OR heliopar:ab,ti OR

- klorokin:ab,ti OR malarex:ab,ti OR malaviron:ab,ti OR mirquin:ab,ti OR nivaquine:ab,ti OR 'novo  
 chloroquine':ab,ti OR novochloroquine:ab,ti OR paluken:ab,ti OR palux:ab,ti OR  
 pharmaquine:ab,ti OR plasmquine:ab,ti OR promal:ab,ti OR 'p roquine':ab,ti OR  
 resoquin\$:ab,ti OR savarine:ab,ti OR syncoquin:ab,ti OR weimerquin:ab,ti
- #26. chloroquine\*:ab,ti
- #25. 'chloroquine'/de
- #24. gold:ab,ti
- #23. 'gold therapy'/de
- #22. axokineor:ab,ti OR dolquine:ab,ti OR ercoquin:ab,ti OR evoquin:ab,ti OR hcqs:ab,ti OR hqt:ab,ti  
 OR hydrocad:ab,ti OR hydroquin:ab,ti OR ilinol:ab,ti OR immard:ab,ti OR metirel:ab,ti OR  
 narbon:ab,ti OR oxcq:ab,ti OR oxiklorin:ab,ti OR 'oxy q':ab,ti OR plaquenil:ab,ti OR  
 polirreuminor:ab,ti OR quensyl:ab,ti OR reuquinol:ab,ti
- #21. hydroxychloro\*:ab,ti
- #20. 'hydroxychloroquine'/de
- #19. salazosulfapyridine:ab,ti OR sulfasalazine:ab,ti OR sulfosalazine:ab,ti OR sulfasazine:ab,ti OR  
 sulfasizine:ab,ti OR salazopyridin\*:ab,ti OR asulfidine:ab,ti OR azulfadine:ab,ti OR  
 azulfidine:ab,ti
- #18. sulfasalazine:ab,ti
- #17. 'salazosulfapyridine'/de
- #16. afiancen:ab,ti OR arabloc:ab,ti OR arava:ab,ti OR artilab:ab,ti OR artrimod:ab,ti OR  
 filartros:ab,ti OR immunoartro:ab,ti OR lefluar:ab,ti OR leflucross:ab,ti OR lefno:ab,ti OR  
 lefra:ab,ti OR lefumide:ab,ti OR lisifen:ab,ti OR molagar:ab,ti OR repso:ab,ti OR rumalef:ab,ti
- #15. isoxazole\*:ab,ti
- #14. 'isoxazole derivative'/exp
- #13. ametopterin:ab,ti OR amethopterin:ab,ti OR abitrexate:ab,ti OR 'a metopterin':ab,ti OR 'a  
 methopterin':ab,ti OR antifolan:ab,ti OR emtexate:ab,ti OR emtrexate:ab,ti OR enthexate:ab,ti  
 OR farmitrexate:ab,ti OR folex:ab,ti OR ledertrexate:ab,ti OR methoblastin:ab,ti OR  
 methohexate:ab,ti OR methotrate:ab,ti OR methylaminopterin:ab,ti OR metotrexat\*:ab,ti OR  
 mtx:ab,ti OR novatrex:ab,ti OR rheumatrex:ab,ti
- #12. methotrexate:ab,ti
- #11. 'methotrexate'/de
- #10. 'disease modifying antirheumatic':ab,ti OR 'disease modifying antirheumatics':ab,ti
- #9. dmard\*:ab,ti
- #8. antirheumatic\*:ab,ti
- #7. 'disease modifying antirheumatic drug'/de
- #6. #3 OR #4 OR #5

- #5. ((early OR recent\* OR undifferentiated OR persistent OR unclassified) NEAR/3 arthritis):ab,ti
- #4. 'rheumatoid arthritis'/exp AND (early:ab,ti OR recent:ab,ti)
- #3. #1 AND #2
- #2. 'early diagnosis'/de
- #1. 'rheumatoid arthritis'/exp