SUPPLEMENTARY APPENDIX 1: MEDLINE SEARCH STRATEGY (JANAURY 2000-JUNE 2010)

1	arthritis, rheumatoid/
2	caplan syndrome/
3	Felty's Syndrome/
4	rheumatoid nodule/
5	exp rheumatoid factor/
6	(arthrit* adj2 rheum*).mp.
7	(caplan* adj2 syndrome*).mp.
8	(felty* adj2 syndrome*).mp.
9	rheumatoid.mp.
10	inflammatory arthritis.tw.
11	or/1-10
12	antirheumatic agents/ or auranofin/ or aurothioglucose/ or azathioprine/ or chloroquine/ or cyclophosphamide/ or cyclosporine/ or gold sodium thiomalate/ or gold sodium thiosulfate/ or hydroxychloroquine/ or interleukin 1 receptor antagonist protein/ or interleukin-4/ or levamisole/ or methotrexate/ or sulfasalazine/
13	(antirheumat* adj2 agent?).mp.
14	(anti-rheumat* adj2 agent?).mp.
15	(antirheumat* adj2 drug?).mp.
16	(anti-rheumat* adj2 drug?).mp.
17	(antirheumat* adj2 therap*).mp.
18	(anti-rheumat* adj2 therap*).mp.
19	dmard.mp.
20	dmards.mp.
21	exp Steroids/
22	exp Adrenal Cortex Hormones/
23	adrenal cortex hormone*.mp.
24	abatacept.mp.
25	abatacept.rn.
26	"ctla-4".mp.
27	orencia.mp.
28	adalimumab.mp.

29	adalimumab.rn.
30	humira.mp.
31	anakinra.mp.
32	anakinra.rn.
33	kineret.mp.
34	ridaura.mp.
35	azathioprine.mp.
36	azasan.mp.
37	imuran.mp.
38	betamethasone.mp.
39	chloroquine.mp.
40	aralen.mp.
41	cyclophosphamide.mp.
42	procytox.mp.
43	cyclosporine.mp.
44	gengraf.mp.
45	neoral.mp.
46	sandimmune.mp.
47	dexamethasone.mp.
48	decadron.mp.
49	depomedral.mp.
50	etanercept.mp.
51	etanercept.rn.
52	enbrel.mp.
53	gold sodium.mp.
54	aurolate.mp.
55	"solu-cortef".mp.
56	hydroxychloroquine.mp.
57	plaquenil.mp.
58	infliximab.mp.
59	remicade.mp.
60	methotrexate*.mp.

61	rhematrex.mp.
62	rheumatrex.mp.
63	trexall.mp.
64	methylprednisolone.mp.
65	medrol.mp.
66	"depo-medrol".mp.
67	"a-methapred".mp.
68	"solu-medrol".mp.
69	"depmedalone".mp.
70	duralone.mp.
71	medralone.mp.
72	prednisone/
73	exp prednisolone/
74	prednisolone.mp.
75	prednisolon.mp.
76	prednisone.mp.
77	priliximab.mp.
78	primaquine.mp.
79	rituximab.mp.
80	rituximab.rn.
81	"anti-cd20 mab".mp.
82	rituxan.mp.
83	mabthera.mp.
84	sulfasalazine.mp.
85	azulfidine.mp.
86	salazopyrin.mp.
87	triamcinolone.mp.
88	azmacort.mp.
89	kenalog.mp.
90	triesence.mp.
91	trivaris.mp.
92	aristospan.mp.

93	golimumab.mp.
94	golimumab.rn.
95	cnto148.mp.
96	"cnto 148".mp.
97	certolizumab.mp.
98	certolizumab.rn.
99	cdp870.mp.
100	"cdp 870".mp.
101	cimzia.mp.
102	tocilizumab.mp.
103	tocilizumab.rn.
104	actemra.mp.
105	"a-il-6r-mab".mp.
106	ofatumumab.mp.
107	ofatumumab.rn.
108	humax.mp.
109	humaxcd20.mp.
110	"cp-690-500".mp.
111	"cp 690 500".mp.
112	"cp 690,500".mp.
113	baminercept.mp.
114	"bg 9924".mp.
115	"bg9924".mp.
116	"rwj 445380".mp.
117	"rwj445380".mp.
118	"acz 885".mp.
119	"acz885".mp.
120	belimumab.mp.
121	"mm 093".mp.
122	"mm093".mp.
123	atacicept.mp.
124	denosumab.mp.

125	"amg 162".mp.
126	"amg162".mp.
127	"azd 9056".mp.
128	"azd9056".mp.
129	apilimod.mp.
130	"sta 5326".mp.
131	"sta5326".mp.
132	exp Tumor Necrosis Factor-alpha/
133	tumor necrosis factor alpha.mp.
134	"cachectin tumor necrosis factor".mp.
135	tnfalpha.mp.
136	tnf-alpha.mp.
137	"member 2 tnf superfamily".mp.
138	cachectin.mp.
139	Tumor Necrosis Factor-alpha.nm.
140	simponi.mp.
141	ro-actemra.mp.
142	corticosteroid*.mp.
143	glucocorticoid*.mp.
144	corticosterone.mp.
145	hydrocortisone.mp.
146	cortisone.mp.
147	amethopterin*.mp.
148	mexate*.mp.
149	abitrexate*.mp.
150	amethopterin*.mp.
151	"a methopterin*".mp.
152	ametopterin*.mp.
153	antifolan*.mp.
154	emtexate*.mp.
155	emthexate*.mp.
156	emtrexate*.mp.

157	enthexate*.mp.
158	farmitrexate*.mp.
159	folex.mp.
160	ledertrexate.mp.
161	methoblastin*.mp.
162	methohexate*.mp.
163	methotrate*.mp.
164	methylaminopterin*.mp.
165	metotrexat*.mp.
166	mexate*.mp.
167	mtx.mp.
168	novatrex*.mp.
169	tumor necrosis factors/ai
170	170277-31-3.rn.
171	avakine.tw.
172	ifx.tw.
173	revellex.tw.
174	d2e7.tw.
175	anti-tumo?r necrosis factor*.tw.
176	antitumo?r necrosis factor*.tw.
177	anti-tnf*.tw.
178	antitnf*.tw.
179	tumo?r necrosis factor* inhibitor*.tw.
180	tumo?r necrosis factor* antibod*.tw.
181	tumo?r necrosis factor* anti-bod*.tw.
182	receptors, tumor necrosis factor/
183	*tumor necrosis factor/
184	antibodies, monoclonal/
185	anti-interleukin*.tw.
186	antiinterleukin*.tw.
187	interleukin 1 receptor antagonist protein/
188	interleukin-1.tw.

189	il-1ra.tw.
190	il-a.tw.
191	exp immunoconjugates/tu
192	exp antigens, differentiation/tu
193	ctla4lg.tw.
194	ctla-4lg.tw.
195	immunologic factors/
196	tnfr.tw.
197	tnf receptor*.tw.
198	cachectin receptor*.tw.
199	tumo?r necrosis factor receptor*.tw.
200	or/196-199
201	fc.tw.
202	fusion protein*.tw.
203	or/201-202
204	200 and 203
205	or/12-195,204
206	11 and 205
207	limit 206 to human
208	limit 207 to yr=2000 - current
209	exp guideline/
210	health planning guidelines/
211	Clinical Protocols/
212	exp consensus development conference/
213	exp consensus development conferences as topic/
214	Guidelines as Topic/
215	Practice Guidelines as Topic/
216	guideline.pt.
217	practice guideline.pt.
218	guideline?.mp.
219	consensus.mp.
220	Health Planning Guidelines/

221	recommendation?.mp.
222	standard?.mp.
223	st.fs.
224	or/209-223
225	208 and 224

SUPPLEMENTARY APPENDIX 2: COMMONLY USED ABBREVIATIONS

Drugs

ABA T	Abatacept
ADA	Adalimumab
Anti-TNF	Tumor necrosis factor inhibitor
CTZ	Certolizumab pegol
DMARD	Disease-modifying anti-rheumatic drug
ETN	Etanercept
GC	Glucocorticoid
GOL	Golimumab
HCQ	Hydroxychloroquine
IFX	Infliximab
LEF	Leflunomide
MTX	Methotrexate
RTX	Rituximab
SSZ	Sulfasalazine
TCZ	Tocilizumab

Investigations

AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
Anti-CCP	Anti-cyclic citrullinated peptide antibody
CBC	Complete blood cell count
Cr	Creatinine
CRP	C-reactive protein
CXR	Chest x-ray
ESR	Erythrocyte sedimentation rate
Hep B, C	Hepatitis B/C serology
PFT	Pulmonary function test
RF	Rheumatoid factor

Guideline Developers

ACR	American College of Rheumatology
ARA	Australian Rheumatology Association
BSR	British Society for Rheumatology
CADTH	Canadian Agency for Drugs & Technologies in Health
CRI	"Club Rhumatismes et Inflammation" (Subcommittee French Society of Rheumatology)
EULAR	European League Against Rheumatism
FSR	French Society of Rheumatology
GPAC	British Columbia Guidelines and Protocols Advisory Committee
HKSR	Hong Kong Society of Rheumatology
JCR	Japanese College of Rheumatology
NICE	National Institute for Health and Clinical Excellence
RACGP	Royal Australian College of General Practitioners
RCN	Royal College of Nursing (UK)
SAMA	South African Medical Association
SER	Spanish Society of Rheumatology
SIGN	Scottish Intercollegiate Guideline Network

Guideline Appraisal

CPG	Clinical practice guidelines
CS	Consensus statement
R	Recommend (AGREE Guideline Quality Score)
R*	Recommend with provisos (AGREE Guideline Quality Score)
WNR	Would not recommend (AGREE Guideline Quality Score)

Level of Evidence (LOE)

I	Meta-analyses, systematic reviews of RCTs, or individual RCTs
II	Meta-analysis, systematic reviews of observational studies (cohort/case control studies) or individual observational studies OR RCT subgroup/post hoc analyses
III	Non-analytic studies, e.g. case reports, case series
IV	Expert opinion
NR	Not reported

APPENDIX 3: EVIDENCE SUMMARIES FROM INTERNATIONAL RA GUIDELINES USED TO INFORM 2011 CRA RECOMMENDATIONS FOR RA

Recommendation 1 - What are the goals of treatment?

Recommendation	Study type	Study	Country	AGREE	LOE
Remission or low-disease activity					
Remission especially in early RA, though LDA may be an appropriate alternative, especially in patients with long-standing RA	CPG	EULAR 2010	Europe	R	I
Modern rheumatologists would aim for meaningful ACR50 or remission goal of ACR70 and/or DAS28<2.6	CPG	ARA 2010	Australia	R*	NR
Remission or at least low disease activity (treatment with TCZ)	CPG	CRI 2010	France	R*	IV
Remission or low disease activity	CPG	SER 2010	Spain	R*	NR
Remission (II or IV). LDA may be an acceptable alternative in established long-standing disease (I)	CS	Smolen 2010	International	R	(II or IV), I
Remission. Where not possible, to minimize disease activity in order to optimize the chances of preventing progressive damage to joints with subsequent disability.	CPG	NICE 2009	UK	R	NR
An ambitious target, perhaps remission	CS	Kiely 2009	UK	R*	NR
Complete remission. Where not possible, to control disease activity and slow the rate of joint damage. Other treatment goals include alleviation of pain, maintenance of function for essential activities of daily living (ADL) and work, and maximization of quality of life.	CPG	RACGP 2008	Australia	R	IV
DAS-28<2.6 or at least <3.2	CPG	BSR 2006	UK	R	NR
Clinical remission. Where not possible, to minimize disease activity. Treatment should be aimed at controlling inflammation, minimizing joint destruction and radiographic progression while preserving functional and work capabilities, and improving quality of life.	CS	Cardiel 2006	Latin America	R*	NR
To eliminate synovitis and disease activity. Where not possible, to control synovitis and disease activity to the fullest extent possible.	CS	Wolfe 2001	USA, Canada	R*	NR

Minimal/low disease activity					
Minimal disease activity, as remission is a difficult target (in RA>2 years)	CPG	BSR 2009	UK	R	I
To relieve pain and swelling of the joints so that cartilage and bone loss are minimized with improvement in functional quality of life. For disease activity, the aim would be to bring DAS28 below 3.2.	CS	Misra 2008	India	R*	NR
Disease activity goal not specified					
Symptom control, reduction of joint damage, and disability, and maintenance or improvement of QOL. Current therapies seldom achieve remission.	CPG	SIGN 2000	Scotland	R	II

Recommendation 2 - What are poor prognostic features that should be measured at baseline to inform treatment decisions?

Recommendation	Study type	Study	Country	AGREE	LOE
RF and/or CCP, particularly in high levels, high disease activity, swollen joint counts or APR, early occurrence of erosions	CPG	EULAR 2010	Europe	R	NR
Recent-onset disease: Anti-CCP, RF, baseline x-rays, nodules, acute phase markers, HAQ, grip strength, swollen joint count. Established disease: baseline disability, older age, longer disease duration, female gender.	CPG	NICE 2009	UK	R	II
Functional limitation, extra-articular disease, RF positivity, positive anti-CCP antibodies, bony erosions by radiograph	CPG	ACR 2008	USA	R	NR
RF or anti-CCP antibodies, high ESR or CRP levels, early radiographic erosions, presence of swollen and tender joints.	CPG	NICE 2007	UK	R	NR
Early arthritis: number of swollen and tender joints, ESR or CRP, level of rheumatoid factor and anti-CCP antibodies, and radiographic erosions.	CPG	EULAR 2007	Europe	R*	II
Predictors of persistent disease (in undifferentiated arthritis): RF, disease duration, ESR, polyarticular disease, female gender, HLA type 19.	CPG	BSR 2006	UK	R	NR
Early age, high-titer RF, marked elevation ESR/CRP, >20 swollen joints, early erosions, severe functional disability at presentation, genetic markers, extra-articular disease.	CPG	SAMA 2003	South Africa	R*	NR

Recommendation 3 - How often should disease activity be monitored?

Recommendation	Study type	Study	Country	AGREE	LOE
Every 1-3 months if active					
Q1-3 months until target reached (which should be within 3-6 mo)	CPG	EULAR 2010	Europe	R	I
With recent onset active RA, monthly until Rx has controlled the disease to the level previously agreed with the person with RA.	CPG	NICE 2009	UK	R	I
Frequent review, ideally monthly in active disease	CS	Kiely 2009	UK	R*	NR
Every 1-3 months if active, longer if well-controlled					
Therapeutic objective not reached: at least every 3 months Therapeutic objective achieved: at least every 6 months	CPG	SER 2010	Spain	R*	IV
As frequently as monthly in patients with high/moderate disease activity (I), or less frequently (such as 3-6 months) in patients in sustained low disease activity or remission. Annual may suffice for patients in sustained remission if they are informed to consult their rheumatologist if they flare (IV).	CS	Smolen 2010	International	R	I, IV
Annual review for patients with stable disease. In the initial phase of disease, patients need to be seen more frequently.	CPG	BSR 2009	UK	R	II
3-month intervals. However, a shorter interval may be appropriate in patients with recent-onset and/or active RA and a larger interval in patients whose disease is well controlled or in remission.	CS	Pham 2005	France	R*	I
When using biologics, every 3/6 months. No distinction by disease activity					
TNF: No less frequently than every 6 months	CPG	BSR 2010	UK	R	IV
TCZ: Every 3 months	CPG	CRI 2010	France	R*	IV
ABAT: At least once every 3 months	CPG	CRI 2009	France	R*	NR
RTX: Every 3 months	CPG	GLADAR 2008	Latin America	R	NR
RTX: At least once every 3 months	CPG	CRI 2008	France	R*	NR
TNF: No less frequently than every 6 months	CPG	NICE 2007	UK	R	NR
TNF: Infliximab – at each visit; etanercept and adalimumab at 1, 3 months then every 3 months	CPG	FSR 2007	France	R*	Unclear

Different intervals for GP and rheumatologist					
After disease is controlled: every 3-6 months by GP, 6-12 months by specialist	CPG	BC 2006	Canada	WNR	NR

Recommendation 4 - How often should the treatment strategy be adjusted in patients with RA?

Recommendation	Study type	Study	Country	AGREE	LOE
Frequent (Q1-3 month) adjustment until target reached					
As long as the target has not been reached, treatment should be adjusted by frequent (every 1–3 months) and strict monitoring (I). Algorithm provided suggests that major adjustments in therapy (switching or adding a DMARD or biologic) should occur every 3-6 months (NR).	CPG	EULAR 2010	Europe	R	I
Until the desired target is reached, treatment should be adjusted every 3 months.	CS	Smolen 2010	International	R	I

Recommendation 5 - How often should radiographs be ordered?

Recommendation	Study type	Study	Country	AGREE	LOE
Every 6-12 months for the first few years					
Every 6-12 mo in the first few years	CPG	EULAR 2007	Europe	R*	II
No erosion: Every 6-12 mo at least for the first 2 yrs With erosion: If it will affect the management	CPG	BSR 2006	UK	R	NR
Annual					
Annual	CPG	CRI 2010	France	R*	IV
Annual for first 3 years, or when starting Rx with biologics	CPG	SER 2010	Spain	R*	NR
Annually, and potential progression of joint damage be estimated (not scored)	CS	Smolen 2010	International	R	NR
Annual	CPG	CRI 2008	France	R*	IV
Annual	CS	Misra 2008	India	R*	NR
Annual, or longer in long-standing disease	CPG	FSR 2007	France	R*	Unclear
Annual	CS	Cardiel 2006	Latin America	R*	NR

Recommendation 6 - Should therapy be changed in RA patients with adequate clinical response but with unequivocal X-ray progression?

Recommendation	Study type	Study	Country	AGREE	LOE
Therapy should be changed if X-ray progression despite adequate clinical response					
If significant progression is detected on x-rays, the therapeutic objective would not have been reached and a change in treatment would be indicated.	CPG	SER 2010	Spain	R*	NR
Progressive structural damage (erosions and/or narrowing) should prompt a reappraisal of the treatment strategy. Regardless of their DAS28 score, patients may be eligible for TNF antagonist therapy if two consecutive radiographic evaluations show disease progression.	CPG	FSR 2007	France	R*	II
Special cases considered to have indications for biologic agents include those with a clinically adequate response to DMARDs but with progressive erosive disease	CS	Massardo 2009	Latin America	R*	NR
Yes, change in therapy warranted if new structural damage despite low disease activity	CS	Meyer 2007	France	R*	NR
X-ray progression will influence the decision, but may not warrant a change in therapy					
The rapidity of progression of joint damage will impact on the decision making process when deciding to use biologics, including in DMARD naïve patients, but lag periods between clinical response and halting of radiographic damage need to be considered.	CPG	EULAR 2010	Europe	R	II

Recommendation 7 – What is the role of glucocorticoids in the management of RA?

Recommendation		Study type	Study	Country	AGREE	LOE
Systemic						
With Initial therapy	GCs added at low to moderately high doses to synthetic DMARD monotherapy provide benefit as initial short-term treatment	CPG	EULAR 2010	Europe	R	I
	Short-term (oral, IM, or IA) to rapidly improve symptoms in newly diagnosed RA	CPG	NICE 2009	UK	R	I
	In recent onset RA, the use of low-dose oral GC (≤ 10 mg/d) is the recommended DMARD therapy, always in combination with DMARD.	CPG	SER 2007	Spain	R*	I
	In RA < 2 years, CS have an important early role in establishing control of synovitis but long-term use is not justified.	CPG	BSR 2006	UK	R	II
	Used in the short term to suppress disease activity while awaiting the beneficial effects of DMARDs.	CPG	SAMA 2003	South Africa	R*	NR
Managing flares	Short-term Rx for managing flares in recent-onset or established disease (in established RA, only after fully explaining risks and if all other options offered)	CPG	NICE 2009	UK	R	NR
	Very useful as bridge therapy to control symptoms, especially flares and to improve patients QOL until the effects of DMARDs are achieved	CS	Cardiel 2006	Latin America	R*	NR
	Parenteral (IV, IM, IA) therapy may occasionally be necessary to suppress flares.	CPG	SAMA 2003	South Africa	R*	NR
Bridge therapy	In RA of long duration, the use of low-dose oral GC is recommended as anti-inflammatory therapy for symptom control while waiting for DMARDs effect.	CPG	SER 2007	Spain	R*	IV
	In RA < 2 years, CS have an important early role in bridging disease control between different DMARD therapies.	CPG	BSR 2006	UK	R	II
	Very useful as bridge therapy to control symptoms	CS	Cardiel 2006	South Africa	R*	NR

Recommendation		Study type	Study	Country	AGREE	LOE
Other situations	GPs: consider short-term low dose oral corticosteroid treatment when analgesics, omega-3 FA, NSAIDs and or cox-2 inhibitors have failed to achieve symptomatic relief.	CPG	RACGP 2008	Australia	R	I
	Selective use of short duration low dose (5-10 mg/d), in RA of <2 years duration with high disease activity under expert supervision.	CS	Misra 2008	India	R*	NR
	Adding CS to existing therapy is an option after DMARD failure.	CS	Meyer 2007	France	R*	NR
Controversial/ not recommended	Corticosteroids remain controversial because of concerns about toxicity, but many rheumatologists believe that low-dose (<10 mg/d) is effective and safe.	CS	Wolfe 2001	USA, Canada	R*	NR
	Oral CS are not recommended for routine use.	CPG	SIGN 2000	Scotland	R	II
Preferred route	Evidence for effectiveness of IM and IV, but IV may be associated with greater toxicity.	CPG	BSR 2006	UK	R	NR
	IM CS allows control of dose and duration of therapy and may be preferable to oral.	CPG	SIGN 2000	Scotland	R	IV
Dosing/ tapering	If used, dose should be kept to a minimum and tapered in case of remission or low disease activity [guideline for all rheumatic diseases]	CPG	EULAR (GC) 2007	International	R*	IV
	A single daily does should be prescribed first thing in the morning. When tapering, should change to single daily dose before reducing dose.	CPG	SER 2007	Spain	R*	NR
	Lowest possible dose should be used for the shortest possible time.	CPG	SIGN 2000	Scotland	R	IV
Intra-articular						
Should consider IA injections for rapid symptomatic relief.		CPG	RACGP 2008	Australia	R	II
IA steroids if a single or only a few joints are inflamed.		CS	Misra 2008	India	R*	NR
The use of IA GC is essential in the mgmt of joints that are persistently inflamed despite good therapeutic response to DMARDs.		CPG	SER 2007	Spain	R*	NR

Recommendation 8 - When should DMARDs be started?

Recommendation	Study type	Study	Country	AGREE	LOE
As soon as possible					
As early as possible, even if they do not yet fulfill established classification criteria.	CPG	EULAR 2010	Europe	R	I
As soon as possible	CPG	SER 2010	Spain	R*	II
Immediately	CS	Kiely 2009	UK	R*	NR
As soon as possible after a diagnosis of RA is established	CPG	BSR 2006	UK	R	NR
Promptly following rheumatology evaluation. The initial evaluation of RA usually takes one to two rheumatology visits.	CS	Wolfe 2001	USA, Canada	R*	NR
Within 2-4 months of persistent symptoms					
Within 3 months of the onset of persistent symptoms	CPG	NICE 2009	UK	R	NR
Should not be delayed beyond 3 months in spite of adequate treatment with NSAIDs if there is ongoing disease activity	CS	Misra 2008	India	R*	NR
At an early stage, ideally within the first 2–4 months	CS	Cardiel 2006	Latin America	R*	NR
As quickly as possible in patients with ERA once disease has been established for 2 to 3 months, recognizing that not all patients will fulfill the ACR criteria for the diagnosis of RA	CS	Bykerk 2004	Canada	R*	NR
All patients with persistent inflammatory joint disease (>6-8 weeks), preferably within 12 weeks.	CPG	SIGN 2000	Scotland	R	II

Recommendation 9 - Which DMARD(s) should be used first?

Recommendation	Study type	Study	Country	AGREE	LOE
Methotrexate					
Methotrexate is considered the anchor drug and should be used first (based on its efficacy alone or in combination with biologics, and its beneficial long-term safety profile)	CPG	EULAR 2010	Europe	R	I
In people with newly diagnosed active RA, offer a combination of DMARDs as first-line treatment: Methotrexate and at least one other DMARD, plus short-term glucocorticoids.	CPG	NICE 2009	UK	R	I
MTX has become the most popular first-line DMARD agent because of its early onset of action (4 to 6 weeks), good efficacy, favourable toxicity profile, ease of administration, and relatively low cost.	CPG	RACGP 2008	Australia	R	NR
Methotrexate is the 'anchor' drug that should be used first	CS	Misra 2008	India	R*	NR
Methotrexate (MTX) is considered the DMARD of choice for the majority of cases	CS	Cardiel 2006	Latin America	R*	NR
Methotrexate should remain the first-line DMARD for RA because it is effective, has a low incidence of serious side-effects and is of relatively low cost	CS	Maddison 2005	UK	R*	NR
Methotrexate has emerged as the preferred and most frequently used first line therapy	CS	Haraoui 2002	Canada	R*	I
Methotrexate or leflunomide					
MTX and LEF, based on: the speed of action, efficacy, tolerance, and influence of radiographic progression	CPG	SER 2010	Spain	R*	IV
Decision based on DAS 28, RF status and radiographic damage. Usually MTX or LEF recommended first, with exceptions in patients with good prognostic factors, where SSZ/HCQ can be used first and exception in patients with high DAS28, RF+, radiographic damage, where ETN can be used first	CS	Le Loet 2006	France	R*	NR
MTX or LEF, except in some patients with very limited disease activity.	CS	Wolfe 2001	USA, Canada	R*	NR
Methotrexate or sulphasalazine					

Recommendation	Study type	Study	Country	AGREE	LOE
Choice of the first agent is based on the risk:benefit ratio with hydroxychloroquine an option in disease perceived as mild and methotrexate or sulfasalazine in those judged moderate-to severe, or likely to progress	CPG	BSR 2006	UK	R	I
SSz and MTX are the DMARDS of choice due to their more favourable efficacy/toxicity profiles	CPG	SIGN 2000	Scotland	R	I
Algorithm provided to guide choice of therapy					
Decision on which DMARD(s) to use first is based on a combination of variables: disease duration, disease activity, prognostic features. Options include: DMARD monotherapy, DMARD combination therapy or Anti-TNF + MTX.	CPG	ACR 2008	USA	R	IV

Recommendation 10 - Which investigations should be ordered prior to starting treatment with methotrexate?

Recommendation	Study type	Study	Country	AGREE	LOE
AST, ALT, albumin, CBC, Cr, CXR (within previous year). Consider: HIV, Hep B/C, fasting glucose, fasting lipid profile and pregnancy test.	CS	Visser 2009	International	R*	II
CBC, urea, electrolytes, LFT, CXR (unless done within last 6 mo) (IV); PFT in selected patients (II or III); if pre-existing liver disease, liver biopsy 3-4 months after MTX started (II or III).	CPG	BSR 2008	UK	R	IV, (II or III), (II or III)
CBC, Liver transaminases, Cr, Hepatitis B, C (if hepatitis risk factors present, e.g. IV drug abuse, health care personnel).	CPG	ACR 2008	USA	R	IV
CBC, liver and kidney biochemistry, albumin, CXR. If pre-existing liver disease or exposure to liver toxins is suspected liver biopsy should be performed before treatment begins.	CPG	SER 2007	Spain	R*	IV
Liver transaminases (I); CBC, Cr (CrCl), albumin (II); Hep B, C (III); CXR (NR); if Hx of respiratory disease or recurrent symptoms, PFT (DLCO) recommended (NR).	CS	Pavy 2006	France	R*	I, II, III
CBC, AST/ALT, Cr, CXR, Hep B, C (if at risk).	CS	Cardiel 2006	Latin America	R*	NR

Recommendation 11 - What is the optimal dosing strategy for methotrexate?

Recommendation	Study type	Study	Country	AGREE	LOE
ROUTE: Orally, but if ineffective, parenteral might be considered **STARTING DOSE:** 7.5 mg – 10 mg (for 4 weeks) **ESCALATION:** Increase by 2.5-5 mg Q 2-6 weeks **MAXIMUM DOSE:** 25	CPG	SER 2010	Spain	R*	IV
ROUTE: Oral with possible switch to parenteral in case of an insufficient response at the highest tolerable dose **STARTING DOSE:** 10-15 **ESCALATION:** Increase by 5 mg Q 2-4 weeks **MAXIMUM DOSE:** 20-30	CS	Visser 2009	International	R*	I/II
ROUTE: Oral, sc or IM if maximum oral dose not effective or not tolerated **STARTING DOSE:** 5-10 **ESCALATION:** Increase by 2.5-5 mg Q 2-6 weeks **MAXIMUM DOSE:** 25 (rarely 30) **TYPICAL DOSE:** 7.5-25	CPG	BSR 2008	UK	R	IV
ROUTE: Oral, but if >15 mg, parenteral is preferable **TYPICAl DOSE:** 7.5-25	CS	Misra 2008	India	R*	NR
ROUTE: Orally, but subcutaneous/IM administration should be considered if poor compliance, inadequate effectiveness, or gastrointestinal side effects (II) **STARTING DOSE:** Not less than 10 mg (I or II) **ESCALATION:** increase at 6 week intervals up to 20 mg (I or II) **MAXIMUM DOSE:** 20 mg (I or II)	CS	Pavy 2006	France	R*	II, (I or II)
ROUTE: Orally, but subcutaneous/IM administration may be an option when there is intolerance or lack of effect **STARTING DOSE:** 7.5-10 **ESCALATION:** increase weekly depending on response up to 25 mg **TYPICAL DOSE:** 20 or 25 mg weekly	CPG	SAMA 2003	South Africa	R*	NR
ROUTE: Generally oral, but can be administered sc or IM in order to achieve a better tolerability or better drug absorption. **STARTING DOSE:** Generally at 7.5 **MAXIMUM DOSE:** Generally does not exceed 25	CS	Haraoui 2002	Canada	R*	NR

Recommendation 12 - When should combination therapy with traditional DMARDs be used?

Recommendation	Study type	Study	Country	AGREE	LOE
Standard of care as initial therapy in early RA					
In people with newly diagnosed active RA, offer a combination of DMARDs as first-line treatment	CPG	NICE 2009	UK	R	I
Combination therapy is the current standard of care.	CPG	BC 2006	Canada	WNR	NR
Use as initial therapy in certain situations					
Decision on whether to use combination therapy and which combination therapy to use is based on combination of variables: disease duration, disease activity, prognostic features.	CPG	ACR 2008	USA	R	I, IV
Combination therapy should be considered for patients with severe disease activity at disease onset, or in the case of therapeutic failure of MTX or LEF	CS	Cardiel 2006	Latin America	R*	NR
After failure of monotherapy					
Combination therapies with DMARDs may be initiated in a 'sequential step up' approach in patients not responding to monotherapy.	CPG	BSR 2008	UK	R	NR
After failure of MTX monotherapy.	CS	Maddison 2005	UK	R*	NR
In inadequate responders to MTX or LEF	CS	Wolfe 2001	USA, Canada	R*	NR
Monotherapy preferred					
In DMARD naïve patients, monotherapy (with or without GCs) rather than combination therapy of synthetic DMARDs may be applied	CPG	EULAR 2010	Europe	R	I

Recommendation 13 - Which traditional DMARD combinations are preferred?

Recommendation	Study type	Study	Country	AGREE	LOE
Methotrexate as anchor					
Methotrexate and at least one other DMARD, plus short-term glucocorticoids	CPG	NICE 2009	UK	R	I
If using combination, methotrexate is considered the anchor.	CPG	EULAR 2007	Europe	R*	NR
Specific combinations listed (most including MTX)					
Choices include: MTX+HCQ; MTX+LEF; MTX+SSZ; HCQ+SSZ; MTX+SSZ+HCQ.	CPG	ACR 2008	USA	R	I, IV
HCQ+MTX+SSZ	CPG	BC 2006	Canada	WNR	NR
MTX+LEF, MTX+SSZ	CS	Maddison 2005	UK	R*	NR
Triple drug combination with MTX, sulfasalazine, and hydroxychloroquine, or the addition of cyclosporine [to MTX or LEF]	CS	Wolfe 2001	USA, Canada	R*	NR

Recommendation 14 - Should leflunomide be used in combination with methotrexate?

Recommendation	Study type	Study	Country	AGREE	LOE
Is effective					
Is an option if certain patients: disease duration 6-24 months if mod-high disease activity (IV); disease duration >24 months if features of poor prognosis or high disease activity (IV, I if high disease activity).	CPG	ACR 2008	USA	R	I, IV
LEF may be successfully added to MTX in cases of failure of efficacy of MTX monotherapy	CS	Maddison 2005	UK	R*	NR
LEF is clinically efficacious and well tolerated when added to MTX treatment, as both an initial and ongoing treatment for RA	CS	Smolen 2004	International	R*	NR
Is effective, but increased toxicity/use caution					
Methotrexate combined with leflunomide significantly increased the risk of gastrointestinal side effects and hepatotoxicity, with a trend towards more withdrawal as a result of toxicity [as compared to MTX monotherapy]	CS	Visser 2009	International	R*	NR
MTX +LEF is very effective particularly in severe disease, but requires careful monitoring for hepatotoxicity	CS	Misra 2008	India	R*	NR
Treatment is efficacious, but high rate of liver enzyme abnormalities. Therefore extreme caution should be exercised with such a combination.	CS	Haraoui 2002	Canada	R*	NR

Recommendation 15 - In patients being considered for treatment with biologic DMARDs, how should an inadequate response to traditional DMARDs be defined?

Recommendation	Study type	Study	Country	AGREE	LOE
One DMARD or more					
HOW MANY: 1 (if poor prognostic factors); switch to another DMARD strategy if no poor prognostic factors (IV) **WHICH REQUIRED**: MTX (I) **DURATION (months):** NR **DURATION AT TARGET DOSE (months):** NR	CPG	EULAR 2010	Europe	R	I, IV
HOW MANY: 1 **WHICH REQUIRED**: preferably MTX or LEF in monotherapy or combination **DURATION (months):** NR **DURATION AT TARGET DOSE (months):** NR	CPG	SER 2010	Spain	R*	I
HOW MANY: 1 **WHICH REQUIRED**: MTX **DURATION (months):** 3 **DURATION AT TARGET DOSE (months):** NR	CPG	FSR 2007	France	R*	Unclear
HOW MANY: 1 **WHICH REQUIRED**: NR **DURATION (months):** NR **DURATION AT TARGET DOSE (months):** 2-3	CS	Cardiel 2006	Latin America	R*	NR
HOW MANY: 1 **WHICH REQUIRED**: NR **DURATION (months):** NR **DURATION AT TARGET DOSE (months):** NR	CS	Haraoui 2002	Canada	R*	NR
HOW MANY: 1 (2 if toxicity to MTX) **WHICH REQUIRED**: MTX **DURATION (months):** NR **DURATION AT TARGET DOSE (months):** 3	CS	Emery 2001	Europe, USA	R*	NR

Recommendation	Study type	Study	Country	AGREE	LOE
HOW MANY: 1 **WHICH REQUIRED**: NR **DURATION (months):** NR **DURATION AT TARGET DOSE (months):** 3 (5 for IM gold, 6 for PCN, 4 for HCQ)	CS	Wolfe 2001	USA, Canada	R*	NR
At least 2					
HOW MANY: 2 (usually given concurrently) **WHICH REQUIRED**: MTX **DURATION (months):** 6 **DURATION AT TARGET DOSE (months):** 2	CPG	BSR 2010	UK	R	II
HOW MANY: 2 **WHICH REQUIRED**: MTX **DURATION (months):** 6 **DURATION AT TARGET DOSE (months):** 2	CPG	JCR 2009	Japan	R*	NR
HOW MANY: 2 **WHICH REQUIRED**: MTX **DURATION (months):** 3 **DURATION AT TARGET DOSE (months):** NR	CS	Massardo 2009	Latin America	R*	NR
HOW MANY: 2 **WHICH REQUIRED**: MTX **DURATION (months):** 6 **DURATION AT TARGET DOSE (months):** 2	CS	Misra 2008	India	R*	NR
HOW MANY: 2 **WHICH REQUIRED**: MTX **DURATION (months):** 6 **DURATION AT TARGET DOSE (months):** 2	CPG	NICE 2007	UK	R	NR
HOW MANY: 2 **WHICH REQUIRED**: MTX **DURATION (months):** NR **DURATION AT TARGET DOSE (months):** 3	CS	Mok 2006	Hong Kong	R*	NR

Recommendation	Study type	Study	Country	AGREE	LOE
HOW MANY: 2 **WHICH REQUIRED**: MTX **DURATION (months):** 6 **DURATION AT TARGET DOSE (months):** 2	CPG	BSR 2005	UK	R*	NR
HOW MANY: 2 **WHICH REQUIRED**: MTX **DURATION (months):** NR **DURATION AT TARGET DOSE (months):** NR	CPG	RCN 2003	UK	R*	Adapted from BSR 2001
At least 3					
HOW MANY: 3 **WHICH REQUIRED**: NR **DURATION (months):** 6 **DURATION AT TARGET DOSE (months):** 2	CPG	SAMA 2003	South Africa	R*	NR
Number of DMARDs Not Reported					
HOW MANY: NR **WHICH REQUIRED**: NR **DURATION (months):** 3 **DURATION AT TARGET DOSE (months):** NR	CPG	ARA 2010	Australia	R*	NR

Recommendation 16 - Which investigations should be ordered prior to starting treatment with biologic DMARDs? (Table excludes LTBI screening recommendations; for evidence table see Canadian recommendations on safety of pharmacological therapy in RA, published separately)

Recommendation	Study type	Study	Country	AGREE	LOE
TNF: CXR, Hep B/C, HIV (for at risk pts), ANA/Anti-dsDNA **RTX**: Quantitative Igs, RF and B cell levels **ABAT**: Hep B/C, HIV (for at risk pts)	CPG	ARA 2010	Australia	R*	NR
TCZ: CBC, transaminases, lipid profile**,** SPEP, CXR, Hep B/C (even if prev performed), HIV within last 5 years unless high risk, IGgs (if prior RTX)	CPG	CRI 2010	France	R*	IV
TNF, ANAK, ABAT, RTX, ABAT: CBC, Hep B/C, CXR, **RTX**: Quantitative IGs	CPG	SER 2010	Spain	R*	NR
ABAT: CBC, SPEP, Hep B/C/HIV (within 5 years unless high risk), CXR	CPG	CRI 2009	France	R*	IV
TCZ: CBC, b-D-glucan	CPG	JCR 2009	Japan	R*	NR
All biologics: CBC, liver transaminases, Cr	CPG	ACR 2008	USA	R	NR
RTX: CXR, CBC, Quantitative Igs, Hep B/C/HIV	CPG	GLADAR 2008	Latin America	R	IV
RTX: EKG, CBC, SPEP, Quantitative Igs, Hep B/C (within 5 years unless high risk), CXR, *recommended:* HIV, B/T cell counts	CPG	CRI 2008	France	R*	IV
TNF: CBC, liver and renal function tests, Hep B/C, routine urine and microscopy, CXR **RTX:** CBC, urea, electrolytes, LFTs, quantitative IGs, Hep B/C.	CS	Misra 2008	India	R*	NR
TNF: CBC, SPEP, transaminases, Hep B/C/HIV, ANA (if + dsDNA), CXR, infection work-up if relevant.	CPG	FSR 2007	France	R*	Unclear
TNF: CXR, LFTs, Hep B/C	CS	Mok 2006	Hong Kong	R*	NR
TNF/ANAK: ANA, CXR	CS	BC 2006	Canada	WNR	NR
TNF: CBC, SPEP, transaminases, Hep B/C/HIV, ANA (if + dsDNA), CXR, infection work-up if relevant.	CPG	CRI 2005	France	R*	IV

Recommendation 17 – Should methotrexate be co-prescribed with biologic DMARDs?

Recommendation	Study type	Study	Country	AGREE	LOE
Use with MTX					
Anti-TNFs are usually combined with MTX, as there is an even greater response to combination therapy	CPG	SAMA 2003	South Africa	R*	NR
Use with MTX; ETN/ADA may be used as monotherapy					
With IFX: yes. Although it is not necessary to co-prescribe methotrexate with etanercept, in patients with inadequate response to etanercept, the addition of methotrexate is a useful option, and vice versa. Similarly, adalimumab may be administered with methotrexate.	CS	Misra 2008	India	R*	NR
TNF inhibitors should normally be used in combination with MTX; if not possible, may use ETN/ADA in monotherapy	CPG	NICE 2007	UK	R	NR
More effective with all, ETN/ADA can be used in monotherapy	CS	Mok 2006	Hong Kong	R*	NR
More effective with all, ETN/ADA can be used in monotherapy	CPG	BSR 2005	UK	R*	NR
ETN/ADA can be used in monotherapy, MTX with IFX	CS	Haraoui 2002	Canada	R*	I
Use with MTX/another DMARD					
Use in combination with MTX or another DMARD. (Only included RCTs of biologic + another DMARD in their analysis)	CPG	CADTH 2010	Canada	R	NR
Anti-TNFs have improved efficacy with respect to excellent clinical responses (ACR 70, remission) and radiological outcomes when used in combination with MTX (I). Anti-TNFs have also been used successfully with other DMARDs, including sulfasalazine and leflunomide (NR).	CS	Furst 2010	International	R*	I, NR
MTX should be prescribed with for IFX; Improved efficacy for ETN/ADA. First reports from the BSR biologic register suggest that efficacy with other agents including leflunomide, ciclosporin and azathioprine.	CPG	BSR 2006	UK	R	NR
Infliximab should be co-prescribed with MTX. A prescribing physician may prescribe alternative DMARDs, although this is outside the recommended product license	CPG	RCN 2003	UK	R*	NR

Recommendation	Study type	Study	Country	AGREE	LOE
Use with MTX/another DMARD; ETN/ADA may be used as monotherapy					
Anti-TNF should be combined with MTX (or other DMARDs) (I). ADA/ETN licensed as monotherapy (NR).	CPG	EULAR 2010	Europe	R	I, NR
ADA/ETN approved as monotherapy; IFX approved with MTX. Combination of each TNF inhibitor with another DMARD, usually MTX, is associated with superior efficacy (eg ACR70, EULAR remission goal) and improved radiological outcomes	CPG	ARA 2010	Australia	R*	NR
MTX (or another DMARD) generally recommended for ETN/IFX/ADA. For ETN/ADA may use in monotherapy.	CPG	FSR 2007	France	R*	I

Recommendation 18 – When should Anti-TNF therapy be used in the treatment of patients with RA?

Recommendation	Study type	Study	Country	AGREE	LOE
After DMARD failure, No comment in naïve					
Patients should have used 2 DMARDs, unless contraindications to DMARDs	CS	Massardo 2009	Latin America	R*	NR
Patients should have failed to respond or tolerate adequate therapeutic trials of at least two standard DMARDs.	CS	Misra 2008	India	R*	NR
Patients are eligible for Anti-TNF therapy if they have undergone trials of two disease-modifying anti-rheumatic drugs	CPG	NICE 2007	UK	R	NR
Indications for TNF antagonists are: treatment of active RA, after a proven therapeutic failure with a DMARD. May be used as first-line therapy if DMARD contraindicated.	CS	Cardiel 2006	Latin America	R*	NR
Indications: Failure of at least 3 previous DMARDs	CPG	SAMA 2003	South Africa	R*	NR
Anti-TNF may be used after a full trial of an effective DMARD such as MTX has shown to be inadequate (for efficacy, safety or tolerability).	CS	Haraoui 2002	Canada	R*	NR
Use in DMARD naïve patients is an option					
DMARD naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological agent	CPG	EULAR 2010	Europe	R	II
In patients with severe, active, progressive RA (may use in DMARD naïve)	CPG	SER 2010	Spain	R*	NR
TNFa blocking agents can be used as the first DMARD in some patients	CS	Furst 2010	International	R*	I

Recommendation	Study type	Study	Country	AGREE	LOE
We recommend initial therapy with a fast-acting component such as step-down corticosteroids or anti-TNF drugs in combination with DMARDs	CS	Kiely 2009	UK	R*	NR
In RA < 6 months duration: 1) If high disease activity for 3-6 months, or 2) If high disease activity for <3 months, poor prognostic factors and no cost or insurance limitations	CPG	ACR 2008	USA	R	IV
In exceptional cases if there is early and severe structural damage	CPG	FSR 2007	France	R*	I
Insufficient evidence to recommend use in DMARD naïve patients					
Other anti-TNF agents can work well with MTX in DMARD naïve patients, there is no evidence to suggest that this approach is cost-effective.	CPG	BSR 2010	UK	R	II
Insufficient evidence to make a recommendation on the use of Anti-TNF therapy in MTX naïve patients	CPG	CADTH 2010	Canada	R	NR
In circumstances when other DMARDs are relatively contraindicated, anti-TNF therapy may be considered in DMARD naïve patients. However, before there is any policy regarding financial subsidy for patients to use the TNF inhibitors from the local public health sector, it is premature at this juncture to make any recommendations on this aspect.	CS	Mok 2006	Hong Kong	R*	NR
On present evidence, our recommendation is that these drugs be used after failure of at least one DMARD	CS	Emery 2001	Europe, USA	R*	NR
No. However, recent reports regarding etanercept in recent onset RA suggest that anti-TNF agents may play a future role as first line treatments of RA.	CS	Wolfe 2001	USA, Canada	R*	NR
At present, patients eligible for TNF-blocking agents are those with an inadequate response to one or more DMARDs, including MTX	CS	Smolen 2000	Europe	WNR	NR

Recommendation 19 - When should abatacept be used in the treatment of patients with RA?

Recommendation	Study type	Study	Country	AGREE	LOE
After DMARD-IR or Anti-TNF-IR					
In patients responding insufficiently to MTX and/or other synthetic DMARDs, biological DMARDs should be started. Current practice would be to start a TNF inhibitor. Patients who fail the first TNF inhibitor should receive another TNF inhibitor, ABAT, RTX, or TCZ.	CPG	EULAR 2010	Europe	R	I
After an inadequate response or intolerance to one or more tumor necrosis factor (TNF)-alpha inhibitor therapies or DMARDs	CPG	CADTH 2010	Canada	R	NR
Severe active RA > 6 months, after failure of MTX, another effective DMARD or a TNF.	CPG	ARA 2010	Australia	R*	NR
Recommended for the treatment of active RA as monotherapy or with DMARDs after an adequate trial of MTX or another effective DMARD.	CS	Furst 2010	International	R*	I
Failure of MTX combination therapy or sequential DMARDs, if RA ≥ 6 months, moderate-high disease activity and poor prognostic factors (listed with TNF and RTX as options). (I for high disease activity).	CPG	ACR 2008	USA	R	I, NR
After Anti-TNF-IR					
Moderate to severe disease activity, after failure of one or more Anti-TNF	CPG	SER 2010	Spain	R*	NR
Not recommended					
Not recommended. If patients are currently receiving abatacept, should have the option of continuing	CPG	NICE 2008	UK	R	NR

Recommendation 20 - When should rituximab be used in the treatment of patients with RA?

Recommendation	Study type	Study	Country	AGREE	LOE
After DMARD-IR or Anti-TNF-IR					
In patients responding insufficiently to MTX and/or other synthetic DMARDs, biological DMARDs should be started. Current practice would be to start a TNF inhibitor. Patients who fail the first TNF inhibitor should receive another TNF inhibitor, ABAT, RTX, or TCZ.	CPG	EULAR 2010	Europe	R	I
RTX is effective in patients with an inadequate response to MTX or at least one TNF inhibitor (I); When TNF inhibitors are not suitable (IV); Current evidence on the efficacy of rituximab relates to RF+ patients and divergent ACR responses were seen with rituximab in RF- patients (IV).	CS	Furst 2010	International	R*	I, IV
In patients for whom methotrexate in combination with DMARDs or sequential administration of other nonbiologic DMARDs led to an inadequate response, with high disease activity and features of a poor prognosis (I for high disease activity).	CPG	ACR 2008	USA	R	I, NR
Active RA (DAS28 > 5.1) with inadequate response to multiple DMARDs.	CS	Misra 2008	India	R*	NR
After Anti-TNF-IR					
After an inadequate response or intolerance to one or more tumor necrosis factor (TNF)-alpha inhibitor therapies (as it is only approved by Health Canada for this indication)	CPG	CADTH 2010	Canada	R	NR
Established severe active RA of > 6 months duration whom have had an inadequate response, intolerance or contraindication to TNF inhibitors	CPG	ARA 2010	Australia	R*	NR
Severe active RA after an inadequate response or intolerance to DMARDs including one or more anti-TNF	CPG	SER 2010	Spain	R*	NR
Active (DAS28>3.2) RF-positive RA who have had an inadequate response or intolerance or contraindication to an adequate course with TNF inhibitors (I); No strong evidence to recommend RTX to RF-negative patients, but should still be considered for Rx (I or II).	CPG	GLADAR 2008	Latin America	R	I, (I or II)

Severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other disease-modifying anti-rheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor α (TNF-α) inhibitor therapy.	CPG	NICE 2007	UK	R	NR
1) Failure of at least one Anti-TNF (NR); Before concluding that a patient has not responded to a TNF blocker, attempts should be made to improve the current regimen by optimizing the DMARD or anti-TNF treatment (NR); Evidence relates to RF+ patients (I). 2) Might be considered if contraindication to TNF, particularly if previous B-Cell lymphoma, MS, concomitant vasculitis/overlap syndromes (IV).	CS	Smolen 2007	International	R*	I, IV, NR

Recommendation 21 - How should patients be retreated with rituximab?

Recommendation	Study type	Study	Country	AGREE	LOE
After relapse or with residual disease activity					
After > 6 months, if relapse (eg- increase in DAS >1.6 following response) or if residual disease (eg- DAS>2.6)	CPG	ARA 2010	Australia	R*	NR
After > 6 months, after relapse if response with first infusion (DAS28 increase > 0.6) or persistent disease activity (DAS28 > 3.2, CDAI >10, SDAI >11). Rare exceptions in partial responders/short-lived response, if other treatment options exhausted.	CPG	CRI 2008	France	R*	IV
After 6 months, if residual active disease (DAS28>3.2) or relapse (DAS28 increase>0.6)	CS	Misra 2008	India	R*	NR
After 6 months, if residual disease activity (DAS28 > 3.2, CDAI >10, SDAI >11) or relapse (such as an increase in DAS28 of >0.6 or an equivalent change in disease activity). No data in patients who failed to respond to first course.	CS	Smolen 2007	International	R*	IV
After relapse					
After 6 months, when relapse (DAS28 >= 3.2) after initial response	CPG	GLADAR 2008	Latin America	R	II
No specific recommendation					
Most of the patients who have subsequent courses did so after 6 months, and none earlier than 4 months.	CS	Furst 2010	International	R*	IV
Only if initial response (DAS28 improvement >= 1.2), at no more frequent than Q 6 months	CPG	NICE 2007	UK	R	NR

Recommendation 22 - When should tocilizumab be used in the treatment of patients with RA?

Recommendation	Study type	Study	Country	AGREE	LOE
After DMARD-IR or Anti-TNF-IR					
In patients responding insufficiently to MTX and/or other synthetic DMARDs, biological DMARDs should be started. Current practice would be to start a TNF inhibitor. Patients who fail the first TNF inhibitor should receive another TNF inhibitor, ABAT, RTX, or TCZ.	CPG	EULAR 2010	Europe	R	I
Severe active RA > 6 months, after failure of MTX, another effective DMARD or a TNF.	CPG	ARA 2010	Australia	R*	NR
Rheumatoid arthritis (RA) who have a history of inadequate effectiveness or intolerance during treatment with one or more DMARDs or TNF antagonists.	CPG	CRI 2010	France	R*	IV
Approved for use in moderate-to-severe active RA in adults who are incomplete responders (owing to adverse effects or lack of response) to DMARDs or TNF blocking agents. Effective in patients with IR to DMARDs and Anti-TNF therapy. Can be used as monotherapy in DMARD/MTX-naïve patients.	CS	Furst 2010	International	R*	I
After failure of DMARDs or Anti-TNFs	CPG	JCR 2009	Japan	R*	Unclear
After Anti-TNF-IR and RTX-IR					
Moderate to severe active rheumatoid arthritis after failure of one or more Anti-TNF agents and RTX (unless RTX CI or withdrawn b/c of adverse event). Patients currently taking TCZ, but not meeting this criteria should remain on TCZ.	CPG	NICE 2010	UK	R	NR

Recommendation 23 - Which therapeutic strategy is recommended after failure of 1 Anti- TNF?

Recommendation	Study type	Study	Country	AGREE	LOE
TNF, another MOA, +/- other options					
Patients with RA for whom a first TNF inhibitor has failed, should receive another TNF inhibitor, abatacept, rituximab or tocilizumab. A preference for a particular biological agent in this situation could not be established.	CPG	EULAR 2010	Europe	R	I
Options (with no preference): switch to a second TNF, change dose/interval for IFX, change to another MOA. If being used in monotherapy, should add MTX first.	CPG	SER 2010	Spain	R*	II
Options (optimal next decision not yet known): Switch to a second TNF, change dose/interval for IFX/ADA, add in/changing dose of conventional DMARDs, switch to another class of biologics.	CPG	ARA 2010	Australia	R*	NR
A switch to a 2nd TNF is recommended unless 1) using IFX: change dose/interval first 2) Using monotherapy, add MTX first. Should also consider other treatment options (i.e.- another biologic with a different mechanism of action)	CPG	FSR 2007	France	R*	II
Only another MOA					
Following failure of or intolerance to a first TNF inhibitor, pts may be switched to ABAT or RTX. Insufficient RCT evidence to support switching to a second TNF or dose escalation.	CPG	CADTH 2010	Canada	R	I

Recommendation 24 - Which therapeutic strategy is recommended after failure of 2 Anti-TNFs?

(Note – No guideline specifically addressed this question. Evidence table reflects those guidelines that commented on the efficacy of a 3rd Anti-TNF in patients who fail 2.)

Recommendation	Study type	Study	Country	AGREE	LOE
A 3rd TNF not recommended after failure of 2					
Achieving a significant clinical response with a third anti-TNF is highly unlikely	CPG	SER 2010	Spain	R*	II
Several observational studies suggest that patients who fail to respond to two TNFs are unlikely to benefit from treatment with a third.	CPG	FSR 2007	France	R*	NR

Recommendation 25 – Which therapeutic strategy is recommended after failure of abatacept, rituximab or tocilizumab?

(No Guidelines addressed question)

Recommendation 26 - Should therapy be tapered or withdrawn in RA patients who achieve sustained remission?

Recommendation	Study type	Study	Country	AGREE	LOE
Caution when considering to taper either					
Caution needed to govern decisions to reduce (dose or interval of) synthetic or biologic DMARD therapy in remission, let alone stopping it.	CS	Smolen 2010	International	R	NR
Taper biologic first, Caution with DMARDs					
Biologics: In persistent remission, after tapering GCs, one can consider tapering biologics especially when combined with synthetic DMARD (II). DMARDs: In sustained long-term remission, could be considered, after tapering of GC and biologics, in a shared decision with patient and physician (III).	CPG	EULAR 2010	Europe	R	II, III
In sustained remission 2 options: 1) Maintain Rx; 2) taper or even stop treatment. The timeline is not defined. Reducing or suspending steroids before modifying the dose of biologics is recommended. Reducing dose of concomitant DMARD not recommended before reducing biologic, unless DMARD toxicity	CPG	SER 2010	Spain	R*	IV
Some evidence for tapering anti-TNF					
Anecdotal studies indicate that lowering the dose of TNFs may be successful without loss of effect	CS	Furst 2010	International	R*	II

Recommendation	Study type	Study	Country	AGREE	LOE
Some patients who have responded well to anti-TNF therapy may be able to remain in remission with a reduced dose or frequency of treatment.	CS	Mok 2006	Hong Kong	R*	NR
Some patients who have responded well to anti-TNF therapy may be able to remain in remission with a reduced dose or reduced frequency of treatment.	CPG	BSR 2005	UK	R*	NR
Taper of either may be considered.					
Drugs that are mainly symptomatic (such as non-steroidal anti-inflammatory drugs and prednisone) should be decreased or stopped first. When a prolonged remission is obtained, a reduction in DMARDs and biotherapies can be considered. However, neither the definition of ‘‘prolonged remission’’ nor the optimal reduction schedule is agreed on.	CPG	FSR 2007	France	R*	Unclear
Insufficient evidence to make a recommendation					
Insufficient evidence to make a recommendation on discontinuation of TNFs in remission. No consensus on definition of remission exists.	CPG	CADTH 2010	Canada	R	NR