

Singapore Chapter of Rheumatologists Consensus Statement on the Eligibility for Government Subsidy of Biologic Disease Modifying Antirheumatic Agents for Treatment of Rheumatoid Arthritis (RA)

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Abstract

Introduction: Up to 30% of patients with rheumatoid arthritis (RA) respond inadequately to conventional non-biologic disease modifying antirheumatic drugs (nbDMARDs), and may benefit from therapy with biologic DMARDs (bDMARDs). However, the high cost of bDMARDs limits their widespread use. The Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore aims to define clinical eligibility for government-assisted funding of bDMARDs for local RA patients. **Materials and Methods:** Evidence synthesis was performed by reviewing 7 published guidelines on use of biologics for RA. Using the modified RAND/UCLA Appropriateness Method (RAM), rheumatologists rated indications for therapies for different clinical scenarios. Points reflecting the output from the formal group consensus were used to formulate the practice recommendations. **Results:** Ten recommendations including diagnosis of RA, choice of disease activity measure, initiation and continuation of bDMARD and option of first and second-line therapies were formulated. The panellists agreed that a bDMARD is indicated if a patient has (1) active RA with a Disease Activity Score in 28 joints (DAS28) score of ≥ 3.2 , (2) a minimum of 6 swollen and tender joints, and (3) has failed a minimum of 2 nbDMARD combinations of adequate dose regimen for at least 3 months each. To qualify for continued biologic therapy, a patient must have (1) documentation of DAS28 every 3 months and (2) at least a European League Against Rheumatism (EULAR) moderate response by 6 months after commencement of therapy. **Conclusion:** The recommendations developed by a formal group consensus method may be useful for clinical practice and guiding funding decisions by relevant authorities in making bDMARDs usage accessible and equitable to eligible patients in Singapore.

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting 0.3% to 0.8% of the population worldwide,¹ and is the most common inflammatory arthritis in Singapore.² Suboptimally treated RA may result in irreversible joint damage,^{3,4} serious extra-articular manifestations,⁵ and comorbidities including osteoporosis⁶ and cardiovascular disease,^{7,8} with substantial adverse impact on patients' health status, health-related quality of life, employment and financial status.⁹ Evidence, both locally and from other parts of Asia highlight the substantial disease burden of RA.¹⁰⁻¹³

It is well known that up to 30% of patients do not respond to traditional non-biologic disease modifying antirheumatic drugs (nbDMARD) such as methotrexate (MTX).¹⁴ Biologic disease modifying antirheumatic drugs (bDMARD) that target specific cytokines, immune cells and signalling pathways have broadened treatment options, with the overarching principle of achieving disease remission through "treating to target". Biologics such as tumour necrosis factor (TNF) inhibitors, anti-CD20 monoclonal antibodies (rituximab), interleukin (IL)-6 receptor

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antagonists (tocilizumab) and selective co-stimulation modulator of T-cells (abatacept) can achieve rapid control of disease activity, retard radiographic progression,¹⁵ reduce functional disability,¹⁶ and improve quality of life¹⁷, and are considered cost-effective from a societal perspective¹⁸ in nbDMARD inadequate responders.

However, the high cost of biological therapies restricts their widespread use. Government-assisted subsidies in developed countries and regions such as the United Kingdom, Europe, Canada and Australia have helped patients access bDMARDs with uptake around 13% for Western European countries.¹⁵ In Asia, countries such as Taiwan, Japan, Hong Kong and Korea have policies in place to financially support the use of bDMARDs in needy patients with active disease. Unfortunately, in Singapore, patients often bear the cost of bDMARD therapy. Due to cost constraints, treatment with a bDMARD is often delayed. The Singapore government initiated the Medication Assistance Fund (MAF) in August 2010¹⁹ to provide subsidies for expensive drugs deemed clinically necessary in eligible patients with various chronic diseases. This applies primarily to the public healthcare sector in Singapore. Most biologics are available in restructured hospitals as non-standard drugs and are not available in the Standard Drug List of subsidised medications. There are currently no consistent criteria among different institutions to guide funding decisions for these therapies for RA, which are often left to the individual physician's appeal and the discretion of each institution's authority. Furthermore, given that the national budget for drug subsidies are not unlimited, there is an urgent need to develop a set of systematic national guidelines for clinical eligibility for MAF funding for bDMARD in RA. With the objective of developing eligibility criteria for funding of bDMARDs for treatment of adult patients with RA, the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore formulated a consensus statement by involving a representative group of practising rheumatologists from the public and private sector through formal consensus methodology.

Materials and Methods

A modified form of the Research and Development/University of California at Los Angeles (RAND/UCLA) Appropriateness Method (RAM)²⁰ was used in the development of our recommendations. In lieu of a systematic literature review, a core working group (CWG) (GGT, PPC, ML and JAC) reviewed established international guidelines and recommendations of rheumatology societies on biologic therapies for treatment of RA. The CWG then developed common clinical scenarios simulating those seen in clinical practice and convened a task force panel (TFP) comprising 9 locally recognised rheumatologists from

various restructured government and private hospitals in Singapore who rated each scenario for appropriateness of treatment. This method has been validated and used widely to develop practice guidelines and quality indicators.^{21,22}

Review of Established Guidelines

The CWG reviewed a total of 7 guidelines from the following established institutions: British Society of Rheumatology (BSR),²³ National Institute for Health and Clinical Excellence (NICE),²⁴ Australian Rheumatology Association (ARA),²⁵ Australian Medicare,¹⁸ American College of Rheumatology (ACR)^{26,27} and European League Against Rheumatism (EULAR)^{28,29} (Table 1).

Biologics considered are those registered in Singapore as of August 2012, i.e. abatacept, adalimumab, etanercept, golimumab, infliximab, rituximab and tocilizumab. However, we approached them in classes by mode of action rather than individually. Clinical scenarios were composed of clinical determinants when biologic therapies would be clinically necessary and appropriate for RA patients: 1) RA diagnosis, 2) threshold disease activity, 3) choice of disease activity measure and 4) failure of nbDMARD (duration, number of combinations, type of nbDMARD and mode of administration of MTX). We also included factors for consideration of continuation of biologic therapy: 1) frequency of documentation of disease activity and response, 2) timing of measurement of response and 3) definition of adequate response. We did not include safety and monitoring recommendations as they ought to be standard practice and are covered extensively by others. Other scenarios added after the first rating and face-to-face meeting included the use of subcutaneous MTX in case of inefficacy or gastrointestinal (GI) intolerance with oral administration.

Discussion was limited to patients who had an appropriate use of non-steroidal anti-inflammatory drugs (NSAIDs), systemic glucocorticoids and intra-articular glucocorticoid injections by the treating physician. Scenarios regarding poor prognostic markers were omitted as these are usually used to select MTX-naïve patients for bDMARD therapy, and we were unable to justify the use of limited funds for bDMARD in this group of patients.²⁷

Rating the Appropriateness of Clinical Scenarios by the TFP

For the first round of ratings, the TFP were contacted by email, provided with evidence synthesised from recent guidelines, clinical scenarios and rating instructions. Based on the literature synthesis and their clinical judgment, the TFP individually rated the "appropriateness" of the clinical scenarios using a 9-point Likert appropriateness scale. Disagreement regarding a specific scenario was defined when one-third or more of the panellists rated a scenario

Table 1. Guidelines Reviewed For Evidence Base and Development of Clinical Scenarios

Organisation	Year of Publication	Purpose of Study	Systematic Literature Review (Search End Date)	Appraisal of Evidence/Consensus Method
American College of Rheumatology ²⁷	2012	Best practice	Yes (February 2010)	RAM
American College of Rheumatology ²⁶	2008	Best practice	Yes (February 2007)	RAM
The British Society of Rheumatology (BSR) ²³	2010	Society considered standard of care	Yes (May 2009)	No formal consensus method
European League Against Rheumatism (EULAR) ²⁹	2010	Best practice	Yes (June 2009)	EULAR standard operating procedures for the development of guidelines
National Institute for Health and Clinical Excellence (NICE) ²⁴	2009	Criteria for government reimbursement	Yes (June 2008)	NICE methodology; NCC-CC quality assurance document and systematic review chart
Australian Rheumatology Association (ARA) ²⁵	2011	Society considered standard of care	Details not available	Details not available
Australian Medicare ¹⁸	Details not available (website last updated in May 2012, no listed issue date of documents)	Criteria for government reimbursement	Details not available	Details not available

RAM: RAND/UCLA Appropriateness Method; NCC-CC: National Collaborating Centre for Chronic Conditions

in the lowest 3 points of the appropriateness scale (ordinal scores 1, 2, or 3) and one-third or more of the panellists rated the same scenario in the highest 3 points (ordinal scores 7, 8, or 9). In the absence of disagreement, a median score of 7 to 9 indicated “appropriate”, 4 to 6 indicated “equivocal” while 1 to 3 indicated “not appropriate” for the option defined in the scenario. The dispersion of scores, ranges and median scores were collated. The TFP and the CWG met under the leadership of a moderator (KHL). The results of the first round of ratings were returned to the individual panellists, with summarised results displayed throughout the discussion.

The objectives of this exercise were emphasised. The TFP agreed upon certain definitions on which they based their discussion and subsequent ratings of the scenarios. In cases of disagreement or equivocal response, there was further discussion by panellists with clarification of definitions, ambiguity and rewording of scenarios. A second round of ratings of all the scenarios by the TFP was carried out by email after the face-to-face meeting.

Conversion of Clinical Scenarios to Consensus Statement

A consensus statement was drafted based on the final agreement of appropriateness. Generally, the recommendations included only positive statements; for example, the recommendations focused on when to implement specific therapies rather than when therapies should be avoided.

Results

A total of 9 panellists in the TFP rated the clinical scenarios twice. In the first round of ratings, there was disagreement among panellists with regards to the criteria for RA diagnosis, the number of minimum swollen and tender joints and whether a uniform disease measure should be used. Disagreements also arose regarding the criteria for continued biologic therapy in patients with active RA, namely, the frequency of the Disease Activity Score in 28 joints (DAS28) documentation, the definition of an adequate response and the time frame in which the response should be seen.

During the face-to-face meeting, it was found that the majority of disagreements could be attributed to varying assumptions and different interpretations of the clinical scenarios. Moreover, it was noted that some options were mutually exclusive and some were questions pertaining to thresholds. For example, some panel members rated as “appropriate” that a patient with active RA is considered suitable for biologic therapy if DAS28 ≥ 3.2 and if DAS28 > 5.1 as the threshold of ≥ 3.2 includes the latter category. In view of this, it was clarified that the TFP should choose the minimum threshold in the second round of voting.

In the second round, panellists rerated the amended clinical scenarios. The final consensus statement is in Table 2. These recommendations are ordered by a logical sequence or procedural and chronological hierarchy rather than by importance. Of the 7 guidelines reviewed, the NICE and Australian Medicare were published for the purpose of

Table 2. Final Consensus Statement on Initiation and Continuation of a Biologic DMARD for RA Requiring Government Subsidisation

	Median Agreement Score of Clinical Scenarios on Likert Scale of 9* (Clinical Threshold or Option)
Recommendations Relating to Initiation of bDMARD Therapy	
1. The patient must fulfil either the 1987 ACR or 2010 ACR/EULAR criteria for RA diagnosis.	9
2. Only one uniform disease activity measure should be used (eg. another disease activity measure or different DAS calculations are not interchangeable).	8.5†
3. The patient must have RA of at least moderate disease activity as measured by a DAS28 score ≥ 3.2 and a minimum of 6 swollen and tender joints.	8.5† (DAS28 ≥ 3.2) 7.5† (≥ 6 swollen and tender joints)
4. The patient must have failed a minimum of 2 combinations of nbDMARDs with each combination at optimal dose regimen for at least 3 months (unless contraindicated by documented significant toxicity). ³⁹	9 (2 combinations) 9 (3 months)
5. Optimal combination must include MTX at a dose of ≥ 20 mg/week (unless contraindicated by documented significant toxicity)‡ and any of the following:	9 (include MTX) 7 (dose ≥ 20 mg/week)
• HCQ (6.5 mg/kg)	7.5† (HCQ)
• HCQ + SSZ (≥ 2 g/d)	9 (HCQ + SSZ)
• LEF (≥ 10 mg/d)	9† (LEF)
• CSA (≥ 2 mg/kg/d)	8.5† (CSA)
• SSZ (≥ 2 g/d)	8† (SSZ)
6. If oral MTX fails due to inefficacy or gastrointestinal intolerance, subcutaneous injection of MTX must be used, and the dose must be at least 20 mg/week. If MTX is contraindicated‡, the patient must have failed a minimum of any 2 combinations of the following nbDMARDs to be considered for biologic therapy:	7 (inefficacy); 9 (intolerance); 9 (minimum dose)
• HCQ (6.5 mg/kg)	
• LEF (≥ 10 mg/d)	9 (2 combinations)
• CSA (≥ 2 mg/kg/d)	
• SSZ (≥ 2 g/d)	
• Sodium aurothiomalate (50 mg/week)	
Recommendations Relating to Continuation of bDMARD Therapy	
7. All patients on bDMARD therapy must have DAS28 documented every 3 months. bDMARD therapy cannot be continued unless the patient has at least a EULAR moderate response by 6 months bDMARD commencement. If the patient does achieve EULAR moderate response criteria but disease activity remains moderate to high (i.e. DAS28 ≥ 3.2), it is the rheumatologist's discretion to switch to alternative bDMARD.	9 (3 months) 8 (6th month) 8 (EULAR moderate response) 9 (rheumatologist's discretion to switch)
Recommendations Relating to Options of bDMARD Therapy	
8. Anti-TNF agents should be the first-line bDMARD unless contraindicated. Anti-TNF should be given with in combination with MTX unless contraindicated.	9 (anti-TNF) 9 (in combination with MTX)
9. The least expensive drug should be prescribed taking into consideration patient's unique characteristics and preferences.	9 (least expensive)
10. Second-line bDMARD treatment, in the event of primary or secondary non-response and adverse effects, may be an alternative anti-TNF or another class of bDMARD (abatacept, rituximab, tocilizumab), taking into consideration patient's unique characteristics and is to be determined by the treating rheumatologist.	9

ACR: American College of Rheumatology; bDMARD: Biologic disease modifying antirheumatic drug; CSA: Cyclosporin A; DAS 28: Disease Activity Score in 28 joints; EULAR: European League Against Rheumatism; HCQ: Hydroxychloroquine; LEF: Leflunomide; MTX: Methotrexate; nbDMARD: Non-biological disease modifying antirheumatic drug; RA: Rheumatoid arthritis; SSZ: Sulfasalazine; TNF: Tumour necrosis factor

*Likert scale of 9 (where 1 = very inappropriate and 9 = very appropriate).

†Fewer than 9 responses were obtained.

‡Methotrexate toxicity criteria: refer to Appendix 1.

guiding government reimbursement and clearly spelt out absolute thresholds relating to initiation and continuation of bDMARD therapy. Therefore, these 2 guidelines were discussed in greater detail.

The EULAR, ACR, BSR and ARA guidelines are referenced whenever applicable, as they provide perspectives on the best practice and standard of care in developed nations. As these recommendations are meant for practising rheumatologists both in the locales where they are published and internationally, they were not prescriptive in terms of particular disease activity criteria, monitoring schedule or specific number/type of joint cutoffs.

Consensus 1: The patient must fulfil either the 1987 ACR or 2010 ACR/EULAR criteria for RA diagnosis.

The 1987 ACR criteria for the classification of RA were used to define active RA in most clinical trials of bDMARDs³⁰⁻³⁴ and are incorporated into most established clinical guidelines. Although they distinguish RA patients with established disease from other types of inflammatory arthritis,³⁵ they are insensitive in early RA. The 2010 ACR/EULAR criteria are a validated revised classification with an increased sensitivity in early RA, introduced due to the recognition that early aggressive therapeutic intervention improves clinical outcomes.³⁵ Although it is rare for patients to only meet the 2010 ACR/EULAR criteria and have failed traditional nbDMARD therapy, the TFP voted that patients could fulfil either criteria for RA diagnosis.

Consensus 2: Only one uniform disease activity measure should be used (e.g. another disease activity measure or different DAS calculations are not interchangeable).

Monitoring of RA disease activity entails measuring the overall state of joint and systemic inflammation as well as damage. There has been a concerted effort to develop composite measures for assessing disease activity and to define response and remission. Evidence-based recommendations require clear definitions of disease activity to make rational therapeutic choices. Although it is not possible to mandate the use of a single disease activity score for the individual physician, and different studies have used different definitions, the TFP agreed that it was preferable to have one uniform scale for administrative purposes in order to achieve consistency, as this set of criteria is meant for determining the eligibility for biologics subsidisation.

One validated composite measure for RA disease activity is DAS28, which is calculated by combining information on swollen and tender joint counts, the acute phase response and patient global assessment on a visual analogue scale (VAS). The DAS28³⁶ has been widely used in clinical trials, registries and guidelines, and is suitable for clinical practice

for monitoring RA disease activity.³⁷ Discussion by the TFP concluded that DAS28 was the most appropriate measure. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) results are obtainable within a 24-hour period of the patient's visit at most local institutions. Furthermore, the panel agreed that blood test results obtained within 4 weeks of the assessment date could be used. Computer software and DAS28 online websites can be used to calculate the DAS28 score quickly and easily.

Other measures of disease activity, such as Clinical Disease Activity Index (CDAI) or Routine Assessment of Patient Index Data 3 (RAPID3), are also quantitative and informative in busy clinic settings and do not require laboratory results. However, another reason for choosing DAS28 is because it is also embedded in the assessment of EULAR response criteria. It is prudent to have a consistent measure to facilitate the processes of subsidy application for initiation as well as continuation of biologics.

Consensus 3: The patient must have RA of at least moderate disease activity as measured by a DAS28 score ≥ 3.2 and a minimum of 6 swollen and tender joints.

Both the BSR²³ and ARA²⁵ advocate the use of DAS28 to determine eligibility, and to commence bDMARD in adult patients who have active RA as defined by DAS28 ≥ 3.2 with at least 3 or more tender and 3 or more swollen joints. There was disagreement among the panellists with the cut-off of DAS28 > 5.1 set as the minimal criteria for initiation of biologics. Certainly, patients with high disease activity should be given priority to biologics therapy. The ACR guideline suggested incorporating any of the 5 common composite disease activity instruments, including DAS28, to measure disease activity but did not mandate uniform use of DAS28.²⁷

There are recognised limitations with DAS28, as it excludes involvement of the feet and ankles, and can be unduly affected by ESR and patient global scores. Clinical synovitis assessed by joint counts is a more objective marker of inflammation than patient global VAS. Therefore, the TFP agreed that patients should have a minimum of 6 swollen and tender joints, in addition to a moderate disease activity of DAS28 ≥ 3.2 (Table 3). The criterion of 6 affected joints was chosen as most biologic trials used this threshold as one of the inclusion criteria; furthermore, patients with multiple joints involvement are at greater risk for progressive joint damage.^{31,32,38} Patients with less than 6 swollen and tender joints might also benefit from biological treatment in order to preserve their quality of life and work ability. The TFP debated lower cut-offs of 4 or less joints, and concluded that disease activity criteria should be more stringent for MAF subsidies.

Table 3. European League Against Rheumatism (EULAR) Response Criteria⁶⁹

Baseline DAS28	DAS28 Improvement Over Time Points		
	>1.2	0.6-1.2	<0.6
Low disease activity <3.2	Good	Moderate	No
Moderate disease activity 3.2 – 5.1	Moderate	Moderate	No
High disease activity >5.1	Moderate	No	No

DAS28: Disease Activity Score in 28 joints

Adjunctive treatments such as joint injection, synovectomy and oral steroid requirement should be taken into account in the global assessment of the patient. The Australian Medicare guideline makes a distinction between major active joints (elbows, wrist, knee, ankle, shoulder and/or hip) and other joints. The TFP decided not to discriminate between the specific joints involved, due to lack of evidence.

Consensus 4: The patient must have failed a minimum of 2 combinations of nbDMARDs with each combination at optimal dose for at least 3 months (unless contraindicated by documented significant toxicity).³⁹

The current practice in restructured (government-linked) hospitals is for patients to be offered multiple available nbDMARD combinations, before an application for MAF subsidy is made and granted for bDMARD. Reasons for this include lack of uniform eligibility criteria between institutions, patients' reluctance in going through financial assessment as part of the application process, and concerns over adverse effects of bDMARDs. Nonetheless, there is evidence that about a third of patients with early RA do respond to an adequate trial of MTX⁴⁰ and combination nbDMARDs have a definite role in both early and established RA.^{41,42} It has been shown that in patients who fail traditional nbDMARDs, addition of bDMARD is significantly superior in controlling joint inflammation, retarding radiological progression and improving physical function in both early and long standing RA.⁴³⁻⁴⁵

The NICE guidelines recommend anti-TNF agents (adalimumab, etanercept, infliximab, golimumab and certolizumab-pegol) for highly active RA (DAS28 >5.1) after failing a trial of 2 nbDMARDs, including MTX. An adequate treatment of 1 nbDMARD constitutes 6 months therapy, with 2 months at standard dose²⁴ but whether combination or sequential regimen should be used was not stipulated. The Australian Medicare, however, subsidises bDMARD therapy after failure or intolerance of a 6-month intensive nbDMARD trial with a minimum of 2 nbDMARD either in combination or as sequential monotherapy for at least 3 months each.¹⁸ The EULAR recommendations are less strict in that only failure of 1 or 2 nbDMARDs are required but not necessarily in combination.²⁹

The TFP agreed that 3 months at optimal dose is appropriate based on the onset of action of most nbDMARDs; however the rate of dose escalation is at the discretion of the treating physician. The ACR guideline recommends initiation of biologic agents in nbDMARD-naïve, early RA patients with high disease activity and features of poor prognosis as supported by cost-effectiveness evaluations in the US populations.²⁶ In contrast, the NICE, BSR, Australian Medicare and EULAR guidelines all do not recommend initial biologic therapy in nbDMARD naïve patients.^{23, 24, 29} The EULAR recommends biological treatment after the first failed nbDMARD treatment in case of unfavourable prognostic factors.²⁹

Consensus 5: Optimal combination must include MTX at a dose of ≥ 20 mg/week (unless contraindicated by documented significant toxicity) and any of the following: HCQ (6.5 mg/kg), HCQ + SSZ (≥ 2 g/d), LEF (≥ 10 mg/d), CSA (≥ 2 mg/kg/d), or SSZ (≥ 2 g/d).

As with most international consensus guidelines, the TFP agreed that the optimal nbDMARDs combination should include MTX at a minimum dose of 20 mg/week (agreement score of 7), unless contraindicated by documented significant toxicity.³⁹ If the patient is not able to tolerate 20 mg/week, the highest tolerated dose is considered acceptable.

The NICE guidelines do not specify any preference for nbDMARDs, beyond recommending that MTX should be included. In contrast, the Australian Medicare detailed an algorithm that all patients must receive MTX alone or in combination therapy or sequential monotherapy with the following alternative nbDMARDs: hydroxychloroquine (HCQ) or leflunomide (LEF) or sulfasalazine (SSZ). If patients cannot take MTX at the minimum dose due to contraindication or intolerance, patients may receive any 2 of HCQ, LEF or SSZ. Rarely, where treatment with MTX, HCQ, LEF or SSZ is not possible at the minimum dose due to contraindication or intolerance, third-line therapy either with azathioprine, cyclosporin or sodium aurothiomalate monotherapy or in combination can be used.¹⁸

In this consensus, the TFP agreed that the optimal combination may include MTX with any of the following: HCQ 6.5 mg/kg, HCQ + SSZ (≥ 2 g/d), LEF (≥ 10 mg/d), CSA (2 mg/kg/d) or SSZ (≥ 2 g/d). There was not sufficient evidence to support the use of azathioprine or minocycline. These are the commonly available nbDMARDs used locally. The local rheumatologists favour the use of combinations of MTX with LEF or MTX with SSZ and HCQ and would generally try to optimise these regimens where possible before escalating treatment to biologics. Evidence suggests that MTX and SSZ combination is not more effective than MTX monotherapy.^{46,47} Nonetheless, TFP surmised that this combination can be tried as it may be efficacious for

certain patients and SSZ is a relatively affordable and well-tolerated drug. Some patients may not be able to tolerate or afford other options.

Consensus 6: If oral MTX fails due to inefficacy or gastrointestinal intolerance, subcutaneous injection of MTX should be used, and the dose should be at least 20 mg/week. If MTX is contraindicated, the patient must have failed a minimum of any 2 combinations of the following nbDMARDs to be considered for biologic therapy: HCQ (6.5 mg/kg), LEF (≥ 10 mg/d), CSA (≥ 2 mg/kg/d), SSZ (≥ 2 g/d) or sodium aurothiomalate (50 mg/week).

During the face-to-face meeting, the panel discussed the efficacy of parenteral MTX based on their expert opinion. Literature review was performed by the CWG and provided to the TFP who voted on the use of subcutaneous MTX at the second round. The subcutaneous form has increased bio-availability, better efficacy and similar tolerability compared to the oral form, and evidence indicates that subcutaneous administration is significantly more effective than oral administration of the same dose, with similar tolerability and fewer GI adverse effects.^{48,49} The TFP considered subcutaneous MTX as appropriate if there is inefficacy or GI intolerance to oral MTX. The dose of subcutaneous MTX should be at least 20 mg/week, if tolerated.

In case of contraindication to MTX, the TFP agreed that an adequate nbDMARD trial would constitute 2 combinations of the following nbDMARDs: HCQ (6.5 mg/kg), LEF (≥ 10 mg/d), CSA (≥ 2 mg/kg/d), SSZ (≥ 2 g/d) or sodium aurothiomalate (50 mg/week). Intramuscular sodium aurothiomalate was included as an option as it is still used in Singapore under special circumstances in patients who are refractory to other less toxic therapies.

Consensus 7: All patients on biologic therapy should have DAS28 documented every 3 months. bDMARD therapy may be continued if the patient has at least a EULAR moderate response by 6 months after commencement. If the patient does achieve EULAR moderate response criteria but disease activity remains moderate to high (i.e. DAS28 ≥ 3.2), it is at the rheumatologist's discretion to switch to alternative bDMARD.

In order to document objective clinical response, the CWG felt it was necessary to standardise disease monitoring during bDMARD therapy. By voting, the TFP agreed that DAS28 should be documented at least every 3 months, as it was a reasonable time frame for tracking the patients' progress. Monthly documentation would be ideal, but it is not practical in busy clinic settings, while semi-annual assessment is too long for the detection of trends.

Response to treatment should be determined by 6 months after commencement of biologic therapy. The BSR guideline

recommends that although the aim should be to achieve a EULAR good response whenever possible, a EULAR moderate response is adequate for continuation of the initial biologic therapy (Table 3).²³ Panellists concurred that while a EULAR good response is the goal, some patients with refractory disease and a very high baseline disease activity may not be able to achieve this, and a EULAR moderate response should be sufficient to justify continued funding of the therapy. If the patient does achieve EULAR moderate response criteria but disease activity remains moderate-high (i.e. DAS28 ≥ 3.2), the rheumatologist retains his/her discretion to switch to alternative bDMARDs.

Consensus 8: Anti-TNF agents should be the first-line bDMARD unless contraindicated. Anti-TNF should be given in combination with MTX unless contraindicated.

Of the biologic therapies, the use of anti-TNF agents are the most established in terms of clinical experience since the first anti-TNF, etanercept, was approved in 1998. Our TFP agreed that anti-TNF therapy should be offered as first-line biologic therapy unless contraindicated, in spite of evidence of efficacy of abatacept,⁵⁰ tocilizumab³⁴ and rituximab⁵¹ compared to MTX in MTX-inadequate responders. Though abatacept and tocilizumab are now approved as first-line biologic in other countries,^{52,53} our experts opined that the extensive long-term observational data with regards to anti-TNF safety justifies their use as first-line biologics. This recommendation may change in the future when longer-term data of other bDMARDs becomes available. In general, anti-TNF agents are more efficacious when given in combination with MTX compared to monotherapy.^{32,41,54,55}

Consensus 9: The least expensive drug should be prescribed taking into consideration the patient's unique characteristics and preferences.

The administration costs, required treatment dose and product price per dose should be weighed when choosing a bDMARD. As there are differences in the modes of administration and treatment schedules, patient preferences should also be taken into consideration. The TFP also opined that escalation of the dose of anti-TNF above the starting dose is not recommended.

Consensus 10: Second-line bDMARD treatment, in the event of primary or secondary non-response and adverse effects, may be an alternative anti-TNF or another class of bDMARD (abatacept, rituximab, tocilizumab), taking into consideration the patient's unique characteristics, and is to be determined by the treating rheumatologist.

In patients who have failed an initial anti-TNF therapy,

studies have shown that switching to a second alternative anti-TNF therapy can be efficacious.^{56,57} Abatacept, rituximab and tocilizumab may be used as alternatives. The NICE guidelines allows subsidy of tocilizumab as first-line, and abatacept after TNF failure.^{58,59} Abatacept, a T-cell costimulation inhibitor, is safe and effective for the treatment of established RA in patients who fail to respond or have a contraindication to anti-TNF agents.⁶⁰ Studies found that treatment with abatacept provided significant clinical benefits regardless of whether the initial TNF inhibitor was discontinued for primary failure or secondary loss of efficacy.^{61,62} Rituximab, a chimeric monoclonal antibody that acts by depleting B cells, was found to be effective for the management of RA patients who have failed one or more anti-TNF therapies.^{33,63} Tocilizumab with MTX is efficacious in patients with RA refractory to one or more anti-TNF therapies, and has a manageable safety profile.⁶⁴

Discussion

In summary, a consensus statement was derived methodically on the use of bDMARDs for RA patients who require financial assistance in Singapore. An eligible patient should have moderately to highly active RA with a DAS28 ≥ 3.2 plus a minimum of 6 swollen and tender joints, and have failed a minimum of 2 nbDMARD combination treatments lasting at least 3 months each. To qualify for continued therapy, all patients on biologic therapy must have DAS28 documented every 3 months and should demonstrate at least a EULAR moderate response in the sixth month after commencement. Switching to an alternative biologic agent may be done at the rheumatologist's discretion if DAS28 remains ≥ 3.2 . Eligible patients should be given anti-TNF therapies as first-line, in combination with MTX, unless both agents are or either agent is absolutely or relatively contraindicated. An alternative anti-TNF or bDMARD of another class (abatacept, rituximab, tocilizumab) may be used as second-line therapy, following inadequate response.

The consensus statement this study developed may be applied as a set of eligibility criteria to guide government funding agencies in identifying patients most likely to benefit from bDMARD therapies, thereby reducing the burden of RA from active disease and joint damage in Singapore. It is recognised that some patients who do not meet the criteria set forth in this consensus may also benefit from bDMARDs. However, given the limited financial resources, the recommendations prioritised patients with the most significant impairment from active RA for biologic therapy. In general, recommendations for therapeutic intervention are not meant to be used as strict protocols. They should be applied and individualised by the treating rheumatologist according to the patient's comorbidities, unique characteristics and preference.

A modified version of the (RAND/UCLA) Appropriateness Method²⁰ was used in the development of our statement. The consensus methodology used is rigorous in that it is a systematic approach to reaching agreement through evidence-based literature and expert opinion. The original method requires a systematic literature review to be conducted. However, as several established rheumatology societies have extensively reviewed the literature and have published recommendations, we presented a comprehensive review and synthesised the evidence from these established guidelines.^{18,23,25-27,29} A limitation of our evidence review is that the most recent literature may not have been included but we believe it was incorporated in the TFP discussions by expert opinion. In addition, the foreign guidelines took into account local socioeconomic and healthcare structures, which cannot be fully generalised to the Singapore context. However, as cost-effectiveness evaluations of individual bDMARDs are not available locally, a group consensus method such as RAM enables pragmatic considerations and experiences from expert opinion to be incorporated. In addition, the scenarios created by the CWG, who are also rheumatologists, captured a good spectrum of common locally encountered situations. The CWG and TFP had rheumatologists representing both public and private healthcare sectors of Singapore and all had special interest in the treatment of inflammatory arthritis. Although there is a global trend for increased patient participation by including patient representatives in consensus committees for RA guidelines,^{65,66} a patient representative was not included in our current study. However, future consensus statements may consider inclusion of a patient representative. Approximately 10% of the scenarios were left unanswered. On clarification by the CWG, 2 members of the TFP were unaware that a response was required for every option (e.g. if they decided that the first option was appropriate, they should indicate that the other options were inappropriate, but instead they left the other options blank). A sensitivity analysis with the missing responses did not change the results.

Most importantly, the agreement on the appropriateness of intervention for each clinical scenario was generally high, with median score of 9/9 for 15 of 25 items rated (several recommendations comprised multiple items). There were 2 scenarios that were contentious with the lowest median score of 7/9, although still within the defined range of agreement. Panellists were initially divided on whether the optimal MTX dose should be at least 25 mg/week or at least 20 mg/week before failure is documented. Consensus was reached that 20 mg/week is sufficient as the effective MTX dosing in the comparator arms of most clinical trials is approximately 20 mg/week.^{41,55} The second scenario with the lowest agreement score of 7 was the use of subcutaneous MTX, if oral MTX fails due to inefficacy. Consensus was

Table 4. Comparison of Reimbursement Guidelines for the Use of Biologic Agents in RA

	Singapore Chapter of Rheumatologists Proposed Criteria	Hong Kong Samaritan Fund	Korea Reimbursement Guideline	Taiwan ⁶⁸
Criteria for Initiation				
DAS 28	≥3.2	≥5.1	Not required	≥5.1
Number of tender and swollen joints	≥6	Not required	>20 joints or >4 large joints (elbow, wrist, ankle, knee, hip, shoulder)	Not required
Lab test	(as per DAS28)	(as per DAS28)	ESR >28 or CRP >2.0	
nbDMARD trial	At least 2 combination treatments lasting at least 3 months each	At least 4 nbDMARDs for at least 3 months each	More than 2 DMARDs for 6 months (at least 3 months per DMARD)	MTX plus at least one other DMARD (given for 6 months, with at least 2 months at standard dose)
Criteria for Continuation				
Measurement of response	EULAR moderate response	A reduction of DAS28 score by >1.2 compared to baseline or ≤3.2	ESR <28 or CRP <2.0 or 20% ESR, CRP improvement and 50% decrease in number of active joint count (equal to ACR 50 response)	Improvement of DAS28 of 1.2 points or more

ACR: American College of Rheumatology; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; DMARD: Disease modifying antirheumatic drug; EULAR: European League Against Rheumatism; ESR: Erythrocyte sedimentation rate; MTX: Methotrexate; nbDMARD: Non-biological disease modifying antirheumatic drug; TNF: Tumour necrosis factor

reached for all scenarios, except on whether the use of sodium aurothiomalate (gold) 50 mg/week in combination with MTX constitutes an adequate trial of nbDMARD in patients. As no consensus was reached, this was not included in the consensus statement.

While consensus recommendations on best practice have been developed⁶⁷ in parts of Asia, more pragmatic guidance for the purposes of individual government subsidisation are needed. Compared to reimbursement criteria from Taiwan,⁶⁸ Hong Kong and Korea (personal communications), the criteria proposed by our Chapter has some notable differences in criteria for initiation of bDMARD (Table 4). To our knowledge, most criteria proposed by other Asian countries were adapted from either the NICE or Australian Medicare guidelines without incorporating validated consensus methodology.

Conclusion

The recommendations are not to be used in a prescriptive way or replace a physician's clinical judgment. Most importantly, the motivation of the endeavour is to provide standardised clinical eligibility criteria to aid decision for subsidy for initiation and continuation biologic treatment of RA in Singapore, in order to enhance more equitable access to effective treatments. Applicability of these recommendations may be limited to the funding structure (e.g. partial or full subsidy, means testing) and changes in the national healthcare budget. The Chapter's consensus statement will need to be periodically updated as newer evidence on treatment strategies continue to emerge.

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REFERENCES

- Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum* 2006;36:182-8.
- Rheumatoid Arthritis. Health Promotion Board; 2012 Updated 3 April 2012; Available at: <http://www.hpb.gov.sg/HOPPortal/dandc-article/572>. Accessed 1 October 2012.
- Eksioğlu E, Tuncay R, Gurcay E, Bal A, Cakci A. Articular damage in late rheumatoid arthritis. *Clin Rheumatol* 2007;26:314-8.
- van der Heijde DM. Joint erosions and patients with early rheumatoid arthritis. *Br J Rheumatol* 1995;34 Suppl 2:74-8.
- Youssef AA, Machaly SA, El-Dosoky ME, El-Maghraby NM. Respiratory symptoms in rheumatoid arthritis: relation to pulmonary abnormalities detected by high-resolution CT and pulmonary functional testing. *Rheumatol Int* 2012;32:1985-95.
- Westhovens R, Dequeker J. Rheumatoid arthritis and osteoporosis. *Z Rheumatol* 2000;59 Suppl 1:33-8.
- Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Svendsen JH, et al. Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ* 2012;344:e1257.
- Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 2005;52:402-11.

9. Furneri G, Mantovani LG, Belisari A, Mosca M, Cristiani M, Bellelli S, et al. Systematic literature review on economic implications and pharmacoeconomic issues of rheumatoid arthritis. *Clin Exp Rheumatol* 2012;30:S72-84.
10. Lee TJ, Park BH, Son HK, Song R, Shin KC, Lee EB, et al. Cost of illness and quality of life of patients with rheumatoid arthritis in South Korea. *Value Health* 2012;15:S43-9.
11. Ho RC, Fu EH, Chua AN, Cheak AA, Mak A. Clinical and psychosocial factors associated with depression and anxiety in Singaporean patients with rheumatoid arthritis. *Int J Rheum Dis* 2011;14:37-47.
12. Langley PC, Mu R, Wu M, Dong P, Tang B. The impact of rheumatoid arthritis on the burden of disease in urban China. *J Med Econ* 2011;14:709-19.
13. Koh ET, Tan JW, Thong BY, Teh CL, Lian TY, Law WG, et al. Major trends in the manifestations and treatment of rheumatoid arthritis in a multiethnic cohort in Singapore. *Rheumatol Int* 2013;33:1693-703.
14. Saevardottir S, Wallin H, Seddighzadeh M, Ernestam S, Geborek P, Petersson IF, et al. Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. *Ann Rheum Dis* 2011;70:469-75.
15. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. *Arthritis Rheum* 2006;55:864-72.
16. Marra CA, Bansback N, Anis AH, Shojania K. Introduction to economic modeling for clinical rheumatologists: application to biologic agents in rheumatoid arthritis. *Clin Rheumatol* 2011;30:S9-18.
17. Atzeni F, Benucci M, Salli S, Bongiovanni S, Boccassini L, Sarzi-Puttini P. Different effects of biological drugs in rheumatoid arthritis. *Autoimmun Rev* 2013;12:575-9.
18. Medicare. Rheumatoid arthritis. Guide to prescribing biological agents. Australian Government. Department of Human Services. Available at: <http://www.medicareaustralia.gov.au/provider/pbs/drugs2/rheumatoid.jsp#N1002B>. Accessed 10 October 2012.
19. Medication Assistance Fund. Singapore: Ministry of Health; 2012; Updated 9 Jan 2012. Available at: http://www.moh.gov.sg/content/moh_web/home/pressRoom/Parliamentary_QA/2011/medication_assistancefund.html. Accessed 10 January 2013.
20. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P. UCLA Appropriateness Method User's Handbook. Santa Monica, CA RAND; 2006. Available at: http://www.rand.org/pubs/monograph_reports/MR1269/index.html. Accessed 1 September 2013.
21. Hemingway H, Crook AM, Feder G, Banerjee S, Dawson JR, Magee P, et al. Underuse of coronary revascularization procedures in patients considered appropriate candidates for revascularization. *N Engl J Med* 2001;344:645-54.
22. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther* 2005;7:R796-806.
23. Deighton C, Hyrich K, Ding T, Ledingham J, Lunt M, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. *Rheumatology (Oxford)* 2010;49:1197-9.
24. NICE clinical guideline. Rheumatoid arthritis. The management of rheumatoid arthritis in adults. Clinical guidelines 79. London. National Institute for Health and Clinical Excellence, 2009. Available at: <http://publications.nice.org.uk/rheumatoid-arthritis-cg79>. Accessed 1 October 2012.
25. Manghani M, Tymms K, Barrett C. Updated Recommendations for the Use of Biological Agents for the Treatment of Rheumatic Diseases. Australian Rheumatology Association; 6 January 2011. Available from: <http://www.rheumatology.org.au/downloads/FINAL-BiologicalRecommendations060111.pdf>. Accessed 1 October 2012.
26. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008;59:762-84.
27. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:625-39.
28. Bijlsma JW. Optimal treatment of rheumatoid arthritis: EULAR recommendations for clinical practice. *Pol Arch Med Wewn* 2010;120:347-53.
29. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;69:964-75.
30. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999;130:478-86.
31. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003;48:35-45.
32. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumor necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;354:1932-9.
33. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350:2572-81.
34. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008;371:987-97.
35. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580-8.
36. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44-8.
37. Smith N, Ding T, Butt S, Gadsby K, Deighton C. The importance of the baseline Disease Activity Score 28 in determining responders and non-responders to anti-TNF in UK clinical practice. *Rheumatology (Oxford)* 2008;47:1389-91.
38. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Mod Rheumatol* 2009;19:12-9.
39. Toxicity criteria and severity descriptors for the listing of biological agents for rheumatoid arthritis on the PBS. Available at: <http://www.medicareaustralia.gov.au/provider/pbs/drugs1/files/ra-toxicity-criteria-and-severity-descriptors.pdf>. Accessed January 23 2013.
40. van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Coster L, Waltbrand E, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (SweFot trial): 1-year results of a randomised trial. *Lancet* 2009;374:459-66.

41. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;363:675-81.
42. O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996;334:1287-91.
43. Curtis JR, Yang S, Chen L, Park GS, Bitman B, Wang B, et al. Predicting low disease activity and remission using early treatment response to antitumor necrosis factor therapy in patients with rheumatoid arthritis: exploratory analyses from the TEMPO trial. *Ann Rheum Dis* 2012;71:206-12.
44. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50:1400-11.
45. van der Heijde D, Klareskog L, Landewe R, Bruyn GA, Cantagrel A, Durez P, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2007;56:3928-39.
46. Dougados M, Combe B, Cantagrel A, Goupille P, Olive P, Schattenkirchner M, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999;58:220-5.
47. Haagsma CJ, van Riel PL, de Jong AJ, van de Putte LB. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. *Br J Rheumatol* 1997;36:1082-8.
48. Braun J, Kastner P, Flaxenberg P, Wahrlich J, Hanke P, Demary W, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008;58:73-81.
49. Mouterde G, Baillet A, Gaujoux-Viala C, Cantagrel A, Wendling D, Le Loet X, et al. Optimizing methotrexate therapy in rheumatoid arthritis: a systematic literature review. *Joint Bone Spine* 2011;78:587-92.
50. Kremer JM, Russell AS, Emery P, Abud-Mendoza C, Szechinski J, Westhovens R, et al. Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. *Ann Rheum Dis* 2011;70:1826-30.
51. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006;54:1390-400.
52. Abatacept for treating rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs (rapid review of technology appraisal guidance 234). National Institute for Health and Care Excellence, 2013. Available at: <http://www.nice.org.uk/nicemedia/live/14155/63676/63676.pdf>. Accessed 1 September 2013.
53. Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198). National Institute for Health and Clinical Excellence, 2012. Available at: <http://guidance.nice.org.uk/TA247>. Accessed 1 September 2013.
54. Soliman MM, Ashcroft DM, Watson KD, Lunt M, Symmons DP, Hyrich KL. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011;70:583-9.
55. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;54:26-37.
56. Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum* 2007;56:13-20.
57. Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009;374:210-21.
58. Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs. London: National Institute for Health and Clinical Excellence, 2011. Available at: <http://www.nice.org.uk/nicemedia/live/13137/51630/51630.pdf>. Accessed 1 September 2013.
59. Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198). London: National Institute for Health and Clinical Excellence; 2012. Available at: <http://www.nice.org.uk/TA247>. Accessed 18 April, 2013.
60. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005;353:1114-23.
61. Tak PP. A personalized medicine approach to biologic treatment of rheumatoid arthritis: a preliminary treatment algorithm. *Rheumatology (Oxford)* 2012;51:600-9.
62. Schiff M, Pritchard C, Hufstutter JE, Rodriguez-Valverde V, Durez P, Zhou X, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumor necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. *Ann Rheum Dis* 2009;68:1708-14.
63. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006;54:2793-806.
64. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumor necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008;67:1516-23.
65. French T, Hewlett S, Kirwan J, Sanderson T. Different wording of the Patient Global Visual Analogue Scale (PG-VAS) affects rheumatoid arthritis patients' scoring and the overall Disease Activity Score (DAS28): a cross-sectional study. *Musculoskeletal Care* 2013;11:229-37.
66. Bartlett SJ, Hewlett S, Bingham CO 3rd, Woodworth TG, Alten R, Pohl C, et al. Identifying core domains to assess flare in rheumatoid arthritis: an OMERACT international patient and provider combined Delphi consensus. *Ann Rheum Dis* 2012;71:1855-60.
67. Mok CC, Tam LS, Chan TH, Lee GK, Li EK. Management of rheumatoid arthritis: consensus recommendations from the Hong Kong Society of Rheumatology. *Clin Rheumatol* 2011;30:303-12.
68. Bureau of National Health Insurance, Department of Health, Executive Yuan. Drug payment regulations. Taipei, Taiwan. Available at: http://www.nhi.gov.tw/webdata/webdata.aspx?menu=17&menu_id=879&WD_ID=993&webdata_id=2919. Accessed 18 April 2013.
69. van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum* 1998;41:1845-50.

Appendix 1. Methotrexate Toxicity Criteria

Adverse Event	Brief Description of Minimum Grade	NIH Common Toxicity Criteria Grade
Anaemia	Haemoglobin <80 g/L	3 (or higher)
Leukopenia	Total WCC <3 x 10 ⁹ /L	2 (or higher)
Thrombocytopenia	Platelets <50 x 10 ⁹ /L	3 (or higher)
Neutropenia	Total neutrophils <1.0 x 10 ⁹ /L	3 (or higher)
Pericardial effusion/pericarditis	Pericarditis (pericardial rub, ECG changes or chest pain)	2 (or higher)
Thrombosis/embolism	Thrombosis/embolism requiring anticoagulant therapy	3 (or higher)
Alopecia	Pronounced hair loss	2 (or higher)
Rash/desquamation	Scattered macular or papular eruption or erythema with pruritis or other associated symptoms covering <50% of body surface or localised desquamation or other lesions covering <50% of body	2 (or higher)
Diarrhoea	Increase of 4 – 6 stools/day over pretreatment	2 (or higher)
Nausea	Oral intake significantly decreased, and symptoms do not improve with at least 2 of the following measures: 1. Reduction of the methotrexate dose 2. Folinic acid/folic acid supplementation 3. Switching from oral to intramuscular dosing 4. Dividing the methotrexate dose over 12 hours A minimum of 3 doses of methotrexate should have been trialled.	2 (or higher)
Pancreatitis	Abdominal pain with pancreatic enzyme elevation	3 (or higher)
Stomatitis	Painful erythema, oedema or ulcers but able to eat or swallow	2 (or higher)
Vomiting	2 or more episodes per 24 hours over pretreatment	2 (or higher)
Bilirubin	>1.5 x ULN	2 (or higher)
Transaminases	ALT and/or AST >2.5 x ULN or ALT and/or AST >1.5 x ULN on 3 occasions over a 3-month period	2 (or higher)
Increased serum alkaline phosphatase	2.5 x ULN	2 (or higher)
Osteonecrosis (avascular necrosis)	Symptomatic and interfering with function	2 (or higher)
Osteoporosis	Symptomatic and requiring treatment	3 (or higher)

ALT: Alanine transaminase; AST: Aspartate transaminase; ECG: Electrocardiogram; NIH: National Institute of Health; ULN: Upper limit of normal; WCC: White cell count