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.

Key words: Drug therapy, Funding, Management, Practice Guidelines

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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Materials and Methods

A modified form of the Research and Development/University of California at Los Angeles (RAND/UCLA) Appropriateness Method (RAM)\textsuperscript{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.\textsuperscript{21,22}

Review of Established Guidelines

The CWG reviewed a total of 7 guidelines from the following established institutions: British Society of Rheumatology (BSR),\textsuperscript{23} National Institute for Health and Clinical Excellence (NICE),\textsuperscript{24} Australian Rheumatology Association (ARA),\textsuperscript{25} Australian Medicare,\textsuperscript{18} American College of Rheumatology (ACR)\textsuperscript{26,27} and European League Against Rheumatism (EULAR)\textsuperscript{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-naive patients for bDMARD therapy, and we were unable to justify the use of limited funds for bDMARD in this group of patients.\textsuperscript{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...
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 $DAS_{28} \geq 3.2$ and if $DAS_{28} > 5.1$ as the threshold of $\geq 3.2$ 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

<table>
<thead>
<tr>
<th>Recommendations Relating to Initiation of bDMARD Therapy</th>
<th>Median Agreement Score of Clinical Scenarios on Likert Scale of 9* (Clinical Threshold or Option)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must fulfil either the 1987 ACR or 2010 ACR/EULAR criteria for RA diagnosis.</td>
<td>9</td>
</tr>
<tr>
<td>2. Only one uniform disease activity measure should be used (eg. another disease activity measure or different DAS calculations are not interchangeable).</td>
<td>8.5†</td>
</tr>
<tr>
<td>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.</td>
<td>8.5† (DAS28 ≥3.2) 7.5† (≥6 swollen and tender joints)</td>
</tr>
<tr>
<td>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).</td>
<td>9 (2 combinations) 9 (3 months)</td>
</tr>
<tr>
<td>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) • SSZ (≥2 g/d)</td>
<td>9 (include MTX) 7.5† (HCQ) 9 (HCQ + SSZ) 9† (LEF) 8.5† (CSA) 8† (SSZ)</td>
</tr>
<tr>
<td>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: • HCQ (6.5 mg/kg) • LEF (≥10 mg/d) • CSA (≥2 mg/kg/d) • SSZ (≥2 g/d) • Sodium aurothiomalate (50 mg/week)</td>
<td>7 (inefficacy); 9 (intolerance); 9 (minimum dose) 9 (2 combinations)</td>
</tr>
<tr>
<td>Recommendations Relating to Continuation of bDMARD Therapy</td>
<td></td>
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<tr>
<td>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.</td>
<td>9 (3 months) 8 (6th month) 8 (EULAR moderate response) 9 (rheumatologist’s discretion to switch)</td>
</tr>
<tr>
<td>Recommendations Relating to Options of bDMARD Therapy</td>
<td></td>
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<tr>
<td>8. Anti-TNF agents should be the first-line bDMARD unless contraindicated. Anti-TNF should be given in combination with MTX unless contraindicated.</td>
<td>9 (anti-TNF) 9 (in combination with MTX)</td>
</tr>
<tr>
<td>9. The least expensive drug should be prescribed taking into consideration patient’s unique characteristics and preferences.</td>
<td>9 (least expensive)</td>
</tr>
<tr>
<td>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.</td>
<td>9</td>
</tr>
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</table>

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.
Consensus 1: The patient must fulfill 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 bDMARDs and are incorporated into most established clinical guidelines. Although they distinguish RA patients with established disease from other types of inflammatory arthritis, 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. 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 fulfill 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 DAS28 has been widely used in clinical trials, registries and guidelines, and is suitable for clinical practice for monitoring RA disease activity. 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 BSR and ARA 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.

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. 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.
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 naive 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 bioavailability, 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. 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), 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, tocilizumab and rituximab compared to MTX in MTX-inadequate responders. Though abatacept and tocilizumab are now approved as first-line biologic in other countries, 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.

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.33,61 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 \( \geq 3.2 \) 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 \( \geq 3.2 \). 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 Method 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 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.51,55 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
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 developed in parts of Asia, more pragmatic guidance for the purposes of individual government subsidisation are needed. Compared to reimbursement criteria from Taiwan, 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 new evidence on treatment strategies continue to emerge.

**Acknowledgement**

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**REFERENCES**


Appendix 1. Methotrexate Toxicity Criteria

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Brief Description of Minimum Grade</th>
<th>NIH Common Toxicity Criteria Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>Haemoglobin &lt;80 g/L</td>
<td>3 (or higher)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>Total WCC &lt;3 x 10^9/L</td>
<td>2 (or higher)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Platelets &lt;50 x 10^9/L</td>
<td>3 (or higher)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Total neutrophils &lt;1.0 x 10^9/L</td>
<td>3 (or higher)</td>
</tr>
<tr>
<td>Pericardial effusion/periocarditis</td>
<td>Pericarditis (periocardial rub, ECG changes or chest pain)</td>
<td>2 (or higher)</td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>Thrombosis/embolism requiring anticoagulant therapy</td>
<td>3 (or higher)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Pronounced hair loss</td>
<td>2 (or higher)</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>Scattered macular or papular eruption or erythema with pruritis or other associated symptoms covering &lt;50% of body surface or localised desquamation or other lesions covering &lt;50% of body</td>
<td>2 (or higher)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Increase of 4 – 6 stools/day over pretreatment</td>
<td>2 (or higher)</td>
</tr>
</tbody>
</table>
| 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. Folic 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                      | ALT >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