EULAR recommendations for the management of rheumatoid arthritis: what is new in 2017 and its applicability in our local setting

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Abstract: Rheumatoid arthritis (RA) is the most common rheumatic disease being managed by the rheumatologists. With the emergence of the biologic and targeted synthetic disease modifying anti-rheumatic drugs (b/tsDMARDs), the prognosis of RA has improved substantially. However, these novel agents are associated with high cost and untoward effects. International consensus statements for the drug management of RA have been published to guide the practice of rheumatologists. In this article, updates from the 2016 EULAR management recommendations for RA are reviewed and discussed within the context of our local situation in Hong Kong.

Keywords: rheumatoid arthritis, guideline, biologics, targeted therapy, prognosis

1 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown pathogenesis.[1] Although the disease predominantly affects the synovial joints that leads to erosion and deformities, other body systems may also be involved. As a result of chronic inflammation and persistent elevation of the inflammatory cytokines, atherosclerosis is accelerated and RA patients are more prone to cardiovascular complications.[2] Owing to the development of various complications and comorbidities, RA is associated with increased mortality and reduced life expectancy.[3] In a recent local study using the hospital death registry and the population census data, we estimated that the standardized mortality ratio of RA was 1.68, indicating that there was a 68% increase in mortality risk compared to the age and gender matched population. [4] The life expectancy of RA was also estimated to be reduced by 6.9 and 5.2 years in female and male patients respectively, compared to the general population. On the other hand, joint deformity, chronic pain and its associated consequences such as adjustment reaction and depressive symptoms in patients with RA leads to physical and work disability, as well as reduction in quality of life. [5-7].

Treatment of RA should be targeted at amelioration of inflammation so as to retard the rate of joint damage. [1] The major breakthrough in the armamentarium of RA therapies in the past 1-2 decades is the emergence of the biological and targeted synthetic disease modifying anti-rheumatic drugs (bDMARDs and tsDMARDs). These agents are more effective and rapid in reducing joint inflammation and retarding the progression of joint erosion than the conventional synthetic DMARDs (csDMARDs) such as methotrexate (MTX), leflunomide and sulphasalazine.[8] Novel DMARDs, together with the availability of more tools for an early diagnosis of disease, such as the anti-CCP test, musculoskeletal ultrasound and magnetic resonance imaging (MRI), and the treat-to-target principle, have led to a tremendous improvement in the clinical outcome of the disease in the recent decade.[9]

While the availability of b/tsDMARDs has improved the outcome of many RA patients, they are associated with a substantial increase in the health cost.[10] Recommendations for the management of RA from academic and administrative bodies around the world have been published for the practicing rheumatologists. One of these recommendations, the European League of Associations of Rheumatology (EULAR), has been widely adopted in many European and non-European countries. Regular update of the recommendations is being published by the EULAR RA task force. The latest version of the EULAR RA recommendations was finalized and published recently in the journal Annals of the Rheumatic Diseases.

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In this review article, major updates of the 2016 EULAR recommendations as compared to the previous version in 2013[12] are highlighted (summarized in Table 1) and its relevance to our local practice in Hong Kong is discussed.

## 2 Use of csDMARDs at phase I of the therapeutic algorithm

RA should be treated with csDMARD as soon as a diagnosis is made. The benefits of early csDMARD treatment in preventing joint damage have been well confirmed in a large number of patients.[13–15] All csDMARDs enable a better long-term outcome in RA on early as compared to delayed administration. MTX should be a part of the initial treatment strategy, unless contraindicated. The target of therapy is clinical remission. If clinical remission is unlikely to be achieved, at least a low disease activity (LDA) state should be reached after 6 months. Therapy could be modified at 3 months if insufficient improvement is observed.

In the 2016 update of the recommendations,[11] “combination therapy of csDMARDs in DMARD-naïve patients (irrespective of the addition of glucocorticoid [GC])” was removed from phase I of the treatment algorithm; the rationale being clinical trials did not show a real benefit of combination therapy, especially when csDMARD monotherapy was combined with GC in the comparator arms.[16–19] In the trials that showed superiority of combination over monotherapy of csDMARDs, there were issues in the study design and differences in the use of GCs in the study arms.[20,21] Moreover, there was concern on the increased risk of toxicities, albeit mild, of csDMARD combinations versus monotherapy.[18,22] Therefore, MTX monotherapy with bridging GCs should be the initial treatment strategy of RA unless under very exceptional circumstances.

This recommendation on initial MTX monotherapy is in concordance with the consensus statements published by the Hong Kong Society of Rheumatology in 2010.[23] In our consensus, MTX monotherapy should be the first csDMARD strategy of RA. When MTX fails

### Table 1: Summary of the major changes of the updated 2016 EULAR recommendations for the treatment of rheumatoid arthritis

<table>
<thead>
<tr>
<th>Updated EULAR recommendations (2016)</th>
<th>Local consensus of Hong Kong Society of Rheumatology (2010)</th>
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<tbody>
<tr>
<td>“Combination therapy of csDMARDs in DMARD-naïve patients” was removed from phase I of management; MTX monotherapy with bridging GCs should be the initial strategy; stepping up to combination csDMARDs or MTX + bDMARD according to poor prognostic factors.</td>
<td>MTX monotherapy as initial therapy of RA, unless contraindicated. Stepping up either to combination of csDMARDs or MTX + bDMARD if no response after 6 months; did not specify poor prognostic factors.</td>
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<tr>
<td>Bridging GCs - “Low-dose GC” was replaced by “short-term”, that is, GCs can be in different dose regimens and routes, but should be tapered as rapidly as feasible. Bridging GCs should not be used when b/tsDMARDs are administered because of their rapid onset of action.</td>
<td>GCs, given orally, intramuscularly, or intra-articularly, may be used as bridging therapy as appropriate.</td>
</tr>
<tr>
<td>tsDMARDs are alternatives to bDMARDs in MTX failure and in the presence of poor prognostic factors (phase II); switching among b/tsDMARDs in phase III treatment algorithm.</td>
<td>tsDMARDs not available in 2010 and therefore, not mentioned</td>
</tr>
<tr>
<td>b/tsDMARDs should be combined with csDMARDs to achieve a synergistic effect; in patients who are intolerant to or contraindicated for csDMARDs, monotherapy with the IL-6 or Jak inhibitors may have some advantages compared with other bDMARDs.</td>
<td>bDMARDs should be combined with MTX; tsDMARDs not available in 2010 and were not mentioned. Indication of monotherapy of the IL-6 inhibitor not specified.</td>
</tr>
<tr>
<td>Early use of bDMARDs before csDMARDs is unlikely cost-effective when the T2T strategy is in force, and did not find a majority vote among the taskforce members.</td>
<td>Not recommended; MTX should be the initiating and anchoring csDMARD</td>
</tr>
<tr>
<td>Tapering of bDMARD can be considered in patients who have sustained remission, especially if treatment is combined with a csDMARD</td>
<td>No recommendation</td>
</tr>
<tr>
<td>All approved bsDMARDs have similar efficacy and safety as the respective boDMARDs, and should be preferred if the cost is lower.</td>
<td>No recommendation</td>
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MTX = methotrexate; csDMARD = conventional synthetic disease modifying anti-rheumatic drugs; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD; bsDMARD = biosimilar DMARD; boDMARD = biological originator DMARD; T2T = treat-to-target; GC = glucocorticoid
to achieve remission or LDA after 6 months, either combination of csDMARDs (such as triple therapy of MTX, sulphasalazine and hydroxychloroquine or combination of MTX and leflunomide) or addition of a bDMARD should be considered. The EULAR recommendations have a more detailed description on the choice between combination csDMARDs and addition of bDMARDs, the former being indicated in patients without poor prognostic factors, whereas the latter being suggested for those with poor prognostic factors.[11]

However, the strategy of initial MTX monotherapy of the 2016 updated EULAR recommendation is different from that recommended by the APLAR in 2015.[24] In the APLAR recommendations, a combination of csDMARDs should be the first strategy in RA patients with poor prognostic factors. This suggestion has probably taken into consideration that in many less affluent Asian countries, bDMARDs are not readily available and patients are more likely to have delayed presentation of their RA. In such situation, a combination of csDMARDs might offer the best cost-effectiveness in the management of patients with established RA.

3 Use of bridging glucocorticoids for rheumatoid arthritis

The added efficacy of GC when combined with csDMARDs is well known. RCTs have shown similar efficacy of GC with bDMARDs when combined with csDMARDs in early RA patients.[25,26] In the 2013 version of the recommendations,[12] the wordings “low-dose GC (prednisone ≤ 7.5mg/day) should be considered as a part of the initial treatment strategy (in combination with csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible” did not truly reflect the real practice, in which higher dose of oral prednisone (e.g., 30mg/day) as a short course or a single intramuscular / intravenous injection (e.g., methylprednisolone) is being used by different rheumatologists. Therefore, in the updated version of the recommendation,[11] the term “low-dose” was deleted and replaced by “short-term”, that is, “Short-term GC should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible”. It was also emphasized that bridging GCs should not be used when b/tsDMARDs are administered, as the onset of action of the latter are usually rapid and the addition of GCs would increase the risk of infection.[27,28]

4 Use of b/tsDMARDs at phase II of the therapeutic algorithm

With the approval of some of the Jak-inhibitors, such as tofacitinib and baricitinib, for the treatment of RA, these tsDMARDs were included in the 2016 updated recommendation at the phase II of the management algorithm.[11] In patients who do not achieve the treatment target with the first csDMARD strategy after 6 months and in the presence of poor prognostic factors, the addition of bDMARD or tsDMARD as a combination therapy should be considered. However, it was stated that the current practice would be to start a bDMARD because of its longer track record in the management of RA. When a bDMARD or tsDMARD has failed to achieve the treatment target, switching to another bDMARD or tsDMARD should be considered at phase III of the management algorithm.

Both the EULAR and the Hong Kong Society of Rheumatology recommendations did not set hierarchical positioning on whether the anti-TNF or non-anti-TNF bDMARDs should be used as first-line bDMARD for RA.[11,23] This is up to the discretion of the attending rheumatologists considering the contraindications to each bDMARD and the preference of the patients based on the route and frequency of administration, as well as the cost. In our local Samaritan fund subsidy scheme, there is no restriction on the choice of bDMARDs after treatment failure of the csDMARDs except for rituximab, which is indicated for anti-TNF bDMARD non-responders only. The maximum number of bDMARDs to be subsidized is confined to five. The new Jak-inhibitor, tofacitinib, is currently under evaluation by the scheme.

5 Monotherapy of the b/tsDMARDs

In the updated EULAR recommendation,[11] there are statements for monotherapy of b/tsDMARDs. In general, bDMARDs and tsDMARDs should be combined with a csDMARD to achieve a synergistic effect, either clinically or radiologically. For the anti-TNF monoclonal bDMARDs, combination with MTX may help reduce the incidence of neutralizing antibodies.[29] In patients who cannot use csDMARDs as co-medication for contraindications or intolerance, monotherapy with IL-6 or Jak inhibitors may have some advantages compared with other bDMARDs. This is based on the evidence from several RCTs which demonstrated superiority of tocilizumab, tofacitinib and baricitinib monotherapy over MTX monotherapy in terms of clinical response rates.[30—33] On the contrary, there
is no evidence that anti-TNF bDMARDs are more effective than MTX as monotherapy of RA. When the clinical response rates of b/tsDMARD monotherapy are compared with MTX in the fore-mentioned RCTs, the effect size is generally greater with Jak-inhibitors than tocilizumab. However, the Jak-inhibitors have a shorter track record than tocilizumab in terms of long-term safety.

6 Use of b/tsDMARDs before csDMARDs

In the updated EULAR RA recommendation,[11] the practice of early use of bDMARDs before csDMARDs was also discussed. A few investigator-initiated studies that compared the first-line bDMARDs plus MTX with GC plus MTX/csDMARD combination did not show a clear benefit of early bDMARD therapy.[19,26] Moreover, 20–25% of RA patients responded well to MTX monotherapy (with GC) and these patients would have been over-treated with bDMARDs, if they were used as first-line.[34] In a recent RCT, it was shown that an addition of bDMARD in MTX inadequate response patients resulted in a response rate similar to that of early use of bDMARD plus MTX.[35] Therefore, the proposal for early use of bDMARDs is unlikely to be cost-effective when the treat-to-target strategy is in force, and did not find a majority vote among the EULAR taskforce members. However, the strategy of early use of bDMARDs as induction, with subsequent withdrawal, as supported by some strategy trials, warrants further confirmation by additional trials before it could be recommended in practice.

The consensus statements from the Hong Kong Society of Rheumatology also did not recommend early use of bDMARDs in treatment-naïve RA patients before an adequate trial of MTX or other csDMARDs is attempted.[23] Use of bDMARDs before csDMARDs in RA is not supported by our local subsidy scheme.

7 Tapering of the b/tsDMARDs

In the updated EULAR recommendation,[11] it was emphasized that tapering of bDMARD can be considered in patients who have sustained remission, especially if this treatment is combined with a csDMARD, although this statement remained unchanged with the 2013 version. Tapering refers to the reduction of dose or prolongation of administration frequency (“spacing”), and does not necessarily imply discontinuation of bDMARD, as this may lead to disease flare in a majority of patients.[36,37] It is also stated that even if the treatment is stopped and there is an arthritic flare, most patients would recover their previous good outcome on reinstitution of therapy.[37,38] Patients should be counseled on this information at the time of commencement of bDMARD therapy.

According to our Samaritan subsidy scheme, bDMARD has to be discontinued in RA patients when sustained clinical remission is achieved for more than 6 months. When there is a flare of the disease, a re-application for the subsidy scheme can be made. This is based on the consideration of the cost-effectiveness and the limitation of resources. The entry and exit criteria of the Samaritan subsidy scheme are subject to periodic review.

8 Use of biosimilars in the management of RA

Since the publication of the 2013 version of the EULAR recommendations,[12] several biosimilar DMARDs (bsDMARDs) have been approved by the European Medicines Agency (EMA) or Food and Drug Administration (FDA). The footnote to bDMARDs in the 2016 updated recommendations mentioned that all EMA-approved or FDA-approved bsDMARDs have similar efficacy and safety as the respective biological originator DMARDs (boDMARDs), and should be preferred if their cost is lower. Among the anti-TNF bsDMARDs, no difference in clinical efficacy with the boDMARDs is demonstrated by head-to-head trials and meta-analyses.[39—44]

The infliximab biosimilar, Remsima, is recently approved in Hong Kong and this is the first bsDMARD licensed for RA. In view of the higher incidence of reactivation of tuberculosis and the issue of immunogenicity (secondary treatment failure), the use of infliximab as the first anti-TNF bDMARD has tremendously reduced in the past few years.[45] It is anticipated that the infliximab biosimilar will replace the original biologic for its lower cost in the public health care system, and it will predominantly be used for the treatment of inflammatory bowel diseases.

9 Conclusions

With the increasing number of b/tsDMARDs available for the treatment of RA, it is essential to better define the treatment algorithm. The 2016 updated EULAR recommendations have incorporated the Jak-inhibitors and the biosimilar DMARDs in the RA treatment algorithm. While the use of b/tsDMARDs for RA before an adequate
trial of MTX or other csDMARDs is not encouraged, there is no hierarchical positioning in the initial choice of b/tsDMARDs in csDMARD non-responders. However, the current practice is to commence the bDMARDs for their longer experience and more safety data. A combination of b/tsDMARDs with csDMARDs is recommended for the synergistic effects and reduction of immunogenicity. However, in patients who are contraindicated or intolerant to csDMARDs, monotherapy of b/tsDMARDs can be considered. The IL6 and Jak inhibitors have the best evidence to be used as monotherapy for RA. Once clinical remission is achieved, tapering of b/tsDMARDs can be considered. Although the EULAR consensus regards the approved bsDMARDs and boDMARDs to have similar efficacy and safety, the exact role of biosimilar DMARDs in the treatment of RA in our locality remains to be discussed and defined.

References