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[Indonesian Rheumatology Association (IRA) Recommendations for Diagnosis and Management of Rheumatoid Arthritis

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is an autoimmune rheumatic disease which often found in daily practice and requires certain considerations in recognizing clinical appearance also managing the disease as it often causes permanent joint damage, disability, even premature death. This recommendation is expected to become the latest reference for diagnosis and management of RA in Indonesia. **Methods**: The steering committee was formed by the Indonesian Rheumatology Association (IRA) to formulate key questions; conduct literature search, selection, and review; then formulate recommendation statements for diagnosis, therapy, and monitoring of RA. Furthermore, the steering committee determined the level of evidence and grades of the recommendations. After that, the level of agreement (LOA) was determined for each item by panelists including rheumatology consultants who have been appointed by IRA to represent Indonesia regions. **Results**: The steering committee established 30 recommendations including diagnosis, the role of laboratory and radiology tests, general treatment, the use of glucocorticoids, sDMARD, bDMARD, and tsDMARD. This recommendation also discusses guidelines on monotherapy, combination therapy, treatment strategies (treat-to-target), tapering, and continuous clinical remission. Treatment on co-morbidities and complications are also included in brief. **Conclusion**: IRA recommendations regarding the diagnosis and management of RA was made by considering various aspects such as the availability of drugs and supporting facilities, socioeconomic and cultural conditions in Indonesia, as well as the latest research that can be applied to Indonesian population.

1. Introduction

Rheumatoid arthritis (RA) is the most common autoimmune rheumatic disease,[1] also a chronic progressive inflammatory disease that often causes permanent joint damage.[1,2] Systemic inflammation in RA is also associated with extra-articular comorbidities including cardiovascular disease, metabolic syndrome, osteoporosis, interstitial lung disease, infection, malignancy, fatigue, depression and cognitive dysfunction, which can increase morbidity and mortality in RA patients.[3] Around 36% of patients

reported to have worse health condition and were twice as likely to experience limitation in their activities. Furthermore, nearly 30% of patients are more likely to need assistance with personal care compared to individuals without arthritis.[4]

The prevalence and incidence of RA vary from each population. Women have a 2-3 times higher risk of getting RA than men. The prevalence of RA is 0.5-1%, which relatively constant in many populations.[5] The exact prevalence of RA in Indonesia is not known, but currently, it is estimated that no less than 1.3 million people suffer from RA in Indonesia based on the prevalence of RA in the world (0.5-1%) multiply by 268 million people, the total population of Indonesia in 2020.

Early diagnosis and prompt treatment with disease-modifying antirheumatic drugs (DMARDs) are essential to achieve disease control and prevent further joint damage and disability. The greatest challenge for diagnosis is early-onset RA, generally with joint manifestations that are difficult to distinguish from other causes of inflammatory polyarthritis. The most important principle of management in RA is to achieve remission or at least low disease activity (LDA), as the treatment target of RA.[4]

The remission rate in Indonesia is 24.5% based on data from The Indonesia RA National Registry (2019-2020 data from 16 centers in Indonesia).[6] The low remission rate possibly related to several factors, such as delay in diagnosis or delay in referral from primary care to specialist, resulting in delay in DMARD therapy initiation, inadequate cDMARD use, and limited access to biological DMARD (bDMARD).

As the previous recommendation of Diagnosis and Management of RA made in 2014, as well as considering there are various recent research and recommendations from international organizations, it is necessary to revise the recommendation. This recommendation is expected to become the latest reference for diagnosis and management of RA in Indonesia, as it was made by considering various aspects such as the availability of drugs and supporting facilities, socioeconomic and cultural conditions in Indonesia, as well as the recent research that can be applied to Indonesian population.

2. Methods

The steering committee was formed by the Indonesian Rheumatology Association (IRA) to develop key questions, conduct literature search, selection, and review. Literature search was conducted online using several search engines such as *Google Scholar, Pubmed, Science Direct, etc.* Keywords used for literature search consisted: *rheumatoid arthritis, screening, diagnosis, NSAID, steroid, glucocorticoid, laboratory test, education, treatment, synthetic DMARDs, biologic DMARDs, monitoring, complication, disease activity, referral, vaccination, pregnancy, lactation and prognosis.*

Literature was limited to those published in English between 2000-2020. The steering committee formulated recommendation statements through online meetings which were held 6 times. The recommendation was made based on key questions. After that, the steering committee determined the levels of evidence and grades of recommendation. Level of evidence is a hierarchical system of evidence classification based on methodological quality of the design, validity and applicability to patient care. Meanwhile, the grades of recommendation are based on levels of evidence with consideration of the overall level of evidence and the judgment of the steering committee. Grades of recommendation was developed based on considerations of cost, value, preference, feasibility, and risk-benefit assessment, as well as assessment of the quality of available scientific evidence.[7]

The final step was to determine the level of agreement (LOA) by the panelist team who have been appointed by IRA. The panelist team consisted of 32 internal medicine specialists, rheumatology subspecialists who had worked for more than 5 years. The panelist team was asked to give a score on each recommendation with a scale of 0-10. A scale of 0 means there is no agreement at all while a scale of 10 is full agreement, accompanied by comments if the score was below 8. The recommendation with a scale

below 8 will be discussed again by the steering committee, so it can be revised, and then the panelists will be asked again to give LOA assessment.

3. Result

The steering committee agreed in 30 recommendations proposed for the diagnosis and management of RA in 2021 which are presented in table 1.

4. Recommendation statement and discussion

Complete history taking and physical examination should be performed in diagnosis of RA

RA is a disease in which more than 50% of non-rheumatologists can diagnose with a good history taking and physical examination. In the diagnosis of RA, history taking was estimated to play an important role for 64% and physical examination for 71%.[8]

RA classification criteria according to the ACR / EULAR 2010 should be used to diagnose RA

The ACR / EULAR 2010 criteria are intended to assist the classification of RA in the early phase, thereby avoiding late diagnosis. This criteria has a lower specificity of 55%, compared to the 1987 ACR criteria with a much higher sensitivity of 97%. [9]

Patients with a suspicion of RA need to undergo RF examination. If the RF is negative, ACPA examination should be performed

Rheumatoid factor (RF) is an antibody that binds to the Fc portion of immunoglobulin G and it is found in 75-85% of RA patients. RF sensitivity is 69% and specificity is 85%.[10] In patients with diffuse musculoskeletal pain without joint swelling, the predictive value of this test is only about 16%. Meanwhile, in patients with symmetrical polyarticular joint swelling, the RF predictive value will increase to 80%.[11] ACPA is more specific for RA with a specificity value of 97%, sensitivity of 67%, negative predictive value of 61%, and positive predictive value of 100%. More than 35% of patients with negative RF have a positive result on ACPA. Studies have found that combination of ACPA and RF antibody test has a higher diagnostic value compared to RF test alone in early arthritis.[10]

Before starting csDMARD therapy, initial laboratory tests consist of complete blood count, ESR, CRP, liver and kidney function test, screening for hepatitis B & C, and chest X-rays are required.

Before starting therapy with conventional synthetic DMARD (csDMARD), screening tests are required to minimize the risk of drug side effects. In Complete Blood Count (CBC), neutropenia, thrombocytopenia, and leukopenia can be found.[12] Inflammatory biomarkers that are routinely used are C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR). CRP and ESR can also be used to assess disease activity and evaluate treatment.[13]

Abnormal liver function tests usually indicate a disease process in the liver, therefore the use of drugs excreted by the liver should be limited, such as methotrexate (MTX), sulfasalazine, and leflunomide.[12] Likewise, kidney disorders must be considered before administering csDMARD.[14] The incidence of hepatitis B and C infection is also increased in RA patients because it is associated with the use of immunomodulatory drugs. In patients with active or chronic hepatitis B infection, antiviral treatment is recommended to be given for 1-2 weeks before, during, and at least 6 months after stopping TNF-α inhibitor treatment in order to reduce the risk of hepatitis virus reactivation.[15] Chest X-rays are required to screen active lung infections including TB which are a contraindication to MTX and leflunomide therapy.[16]

Before starting bDMARD or tsDMARD therapy, additional IGRA and tuberculin tests are required for TB screening, as well as HIV testing for those at high risk.

Before initiation of biological DMARD (bDMARD) or

targeted synthetic DMARD (tsDMARD) therapy, screening tests in point 4 are required with additional examinations for tuberculosis (TB) screening consist of tuberculin skin test (TST) and interferon-gamma release assays (IGRA), especially before administering TNF-α inhibitor therapy.[12,17] There is a lack of data on the safety of bDMARD and tsDMARD for RA in people with HIV, but HIV test is recommended for those at high risk before starting bDMARD or tsDMARD.[18]

To assess complications of the disease, additional examinations are required, such as joint X-rays, musculoskeletal ultrasound, BMD, laboratory tests, and other supporting examinations as indicated.

On radiological examination, the more specific changes as a characteristic of RA progression are juxta-articular erosion and symmetric joint narrowing. These changes can be seen in the first 6-12 months in the course of the disease.[10,13]

Comorbidities often found in patients with RA are cardiovascular disease, infection, malignancy, osteoporosis, etc, which either occur due to therapy such as glucocorticoids or due to RA itself.[19,20] In cardiovascular disease, it is necessary to monitor blood pressure, blood glucose levels, low-density lipoprotein (LDL), high-density lipoprotein (HDL), cholesterol, and serum creatinine.

Evaluation of osteoporosis in RA patients is necessary. In certain RA conditions, bone mineral density (BMD) examination and vitamin D level test can be performed. Malignancy can also be increased in RA patients. Malignancies that can arise include prostate cancer (PSA examination), breast cancer (mammography), colon cancer (colonoscopy), and lung cancer (chest X-ray).[19]

To assess the side effects of treatment, routine blood tests, liver and kidney function test, and other examination are necessary as indicated

Recommendation interval time for monitoring RA treatment is for < 3 months therapy in every 2-4 weeks, for 3-6 months therapy in every 8-12 weeks and for >6 weeks of therapy in every 12 weeks.

Treatment with hydroxychloroquine/ chloroquine for more than 5 years, require an annual ophthalmology examination.

The goal of RA management is to control disease activity, obtaining remission or at least low disease activity (LDA).

The main objective of RA treatment is to control disease activity, specifically to achieve a remission characterized by the absence of symptoms and signs of significant inflammatory activity.[21]

RA management includes education, medical therapy, and rehabilitation/ exercises programs.

The 3 pillars of RA treatment are:

a) Education;
b) Medical therapy, includes non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional synthetic DMARD (csDMARD), synthetic targeted (tsDAMRD), and biological DMARD (bDMARD);
c) Rehabilitation/ exercises programs.

Modality and drugs for the treatment of RA must be chosen based on a shared decision-making between the patient and the doctor.

Besides knowing about the therapeutic options and the reasons for certain therapeutic recommendations including the benefits and risks, patient should take a role in making the decisions.[21]

Education for the patients includes disease progression, diagnosis and treatment plans, benefits and risks of the therapy, complications, and prognosis.

Cooperation between doctors and patients is very important to improve treatment adherence so that it

will improve treatment outcomes. Research on 100 RA patients for 6 months showed that education provided significant improvements in attitudes, pain, and disabilities in patients.[22]

Therapy with csDMARD should be started immediately after the diagnosis of RA is made, with methotrexate (MTX) as a primary choice. Unless there is contraindication or intolerance with MTX, other csDMARDs can be used including leflunomide, sulfasalazine, chloroquine, hydroxychloroquine, cyclosporine, azathioprine.

Early diagnosis and therapy are the most important steps to control disease progression. Good therapeutic results within the first 6 months of disease onset can predict therapy response over the next 5 years.[23] MTX is the first choice used in RA. It can be used as monotherapy or combination therapy as it has a good efficacy/toxicity ratio.[24,25]

DMARD therapy selection is based on disease activity, drug safety, and patient factors such as comorbidities and progressive structural damage.

The choice of DMARD therapy is determined by 3 factors:

a) Drug factors: effectiveness, ease of administration, monitoring system, the time needed for the drug to provide efficacy, possible side effects, and cost
b) Patient factors: patient adherence, comorbidities, the severity of disease, and possible prognosis
c) Doctor factor: competence in administering and monitoring drugs.

NSAIDs or low-dose glucocorticoids can be given before starting DMARD therapy. The dose is immediately reduced or stopped when DMARD is effective.

Non-steroidal anti-inflammatory drugs (NSAIDs) are used in the initial treatment of RA to reduce pain and swelling. However, its used does not change the course of the disease so it cannot be used as monotherapy. Glucocorticoids are also part of the initial therapy for RA to control the disease quickly, which the dose is gradually reduced when DMARD starts working.[25] In the use of glucocorticoids, side effects must be considered, such as hypertension, fluid retention, hyperglycemia, dyslipidemia, osteoporosis, cataracts, osteoporosis, and early atherosclerosis.[25]

If the treatment target is not achieved within 3-6 months with the first csDMARD, the second csDMARD can be added as combination therapy; or bDMARD can be started as combination therapy or as csDMARD substitution, especially in patients with poor prognostic factors

If treatment target is not achieved with the first csDMARD strategy (monotherapy with optimal dose), in the absence of poor prognostic factors, another csDMARD can be added as a combination therapy. A meta-analysis of the efficacy and toxicity of MTX monotherapy compared to combination therapy of MTX and csDMARDs, involving 5 studies with 552 subjects, showed benefits of csDMARD combination therapy. The study reported that in RA patients with inadequate response of MTX monotherapy, the addition of a second csDMARD was significantly more effective with RR = 2.51 (95% CI 1.92-3.28), RR = 4.54 (95% CI 2.51-8.20) and RR = 5.59 (95% CI 2.08-15.01) for the ACR criteria 20, 50 and 70, respectively. However, the number of patients who withdrew because of toxicity increased by 1.89 (95% CI 1.05 to 3.41) in the combination group. Whereas in the group of patients who had never received DMARD therapy before, combination therapy was not significantly different compared to MTX monotherapy.[26]

In patients with poor prognosis factors, if treatment target is not achieved with the first csDMARD, bDMARD can be started as combination therapy or as a substitute for csDMARD.[27] Some bDMARDs such as TNF-α inhibitor and IL-6 inhibitor had a good effects when combined with MTX in the early stages of RA.[25] TNF-α inhibitor combined with MTX can suppresses disease activity, improves physical function, and

inhibits progressive radiographic damage in RA patients who do not respond to MTX or other csDMARD.[28,29] MTX increases the efficacy of TNF-α inhibitor including etanercept, infliximab, golimumab, and adalimumab.[30] The same effect was observed for certolizumab31 and rituximab[31] and *rituximab*[32]. IL-6 inhibitor, tocilizumab, can provide a remission rate of 35.1% on RA therapy, with a continuation rate for 3 years is 68.2%.[33]

If the treatment target is not achieved within 3-6 months with bDMARD, treatment with another bDMARD or tsDMARD should be considered

If the first bDMARD has failed, treatment with another bDMARD with different mode of action, either with TNF-α inhibitor or IL-6 inhibitor, or an alternatives bDMARD such as CD-20 inhibitor (rituximab) and T cell co-stimulator inhibitor (abatacept). Another option is tsDMARD group, namely the Janus Kinase inhibitor (tofacitinib).

In RA patients with persistent remission for 12 months, consider tapering or stopping bDMARD or tsDMARD especially in combination therapy with csDMARD.

It is important to know that stopping bDMARD is often associated with RA flares (increases with time since discontinuation). Therefore, it is recommended to reduce the dose or increase the interval of therapy rather than stopping treatment. In the majority of patients with flare (>80%), a good response can regain by restoring the previous treatment dose. The estimated flare rates in the meta-analysis study were 0.26 in cases that reduced the dose and 0.49 in cases that stopped TNF-α inhibitor. The flare rates in the 3 studies which discontinue tocilizumab therapy were 41% at 6 months, 55% after 1 year (combination tocilizumab + MTX), and 87% at 1 year (tocilizumab monotherapy). [34]

In patients who achieve persistent remission on csDMARD therapy, a gradual tapering could be considered

Patients who got csDMARD combination therapy can stop one of the csDMARDs when persistent remission has been achieved (at least 12 months).[27] Patients on a csDMARD monotherapy may be considered to reduce the dose gradually. The discontinuation of csDMARD altogether should be reviewed and discussed with the patient because of the significant risk of flare, meanwhile returning to csDMARD therapy (at the original dose) will only give a good response in 50% of cases.[27]

Physiotherapy and physical exercise should be done gradually and regularly to increase muscle strength and joint ROM.

Physical exercise and rehabilitation are important to maintain joint function and muscle strength. Other benefits including reduce cardiovascular risk and bone loss, increase bone density, decrease the progression of radiological changes in small joints, prevent depression, improve sleep quality, reduce pain perception, and improve quality of life.

The recommended physical exercise is walking, cycling and swimming. Start physical exercise with "start low, go slow". Physical exercise is recommended to be done for 30 minutes/day. The American College of Rheumatology and the American Pain Society recommend aerobic and physical exercise that includes flexibility and physical endurance as well as the use of orthotics or splints. [35]

Live vaccines are not allowed to be given to RA patients receiving DMARD therapy

In patients with DMARD therapy, it is recommended to avoid live vaccines because it contains attenuated live microorganisms which could theoretically cause infection in susceptible RA populations. Vaccines that contraindicated in RA populations include MMR,

rubella, oral polio, BCG, yellow fever, oral typhoid fever and herpes zoster.[36,37]

Vaccinations that are recommended before giving DMARD are influenza, pneumococcus, Herpes zoster, Hepatitis B, and HPV.

DMARD is an immunosuppressive agent that can increase the risk of infection, therefore prevention including vaccination must be considered. Vaccines administration should be done before starting DMARD therapy as live vaccines are contraindication once immunosuppressives therapy started, also immune response to vaccines is suboptimal.[24,38,106]

RA patients should be prepared or planned for pregnancy, preferably after achieve low disease activity or remission

Patients with early RA and/ active disease should consider delaying pregnancy until low disease activity or remission achieved and maintained for at least 6 months.[38]

The drug safety should be evaluated for couple planning to have children, as well as during pregnancy, and lactation

In the preconception phase, patients should receive education, especially about the use of RA drugs during pregnancy, education about teratogenicity, and drug side effects. Some drugs, such as MTX and leflunomide, have to be stopped months to years before conception.[39,40]

Disease activity should be evaluated more closely in the postpartum period, because of the increased risk of recurrence

About 90% of women with RA will experience a relapse during the postpartum period, usually within the first three months after delivery. It is associated with the possibility of increased prolactin (proinflammatory hormone) levels, changes in the neuroendocrine axis and in Th2 to Th1.[40] Many experts recommend restarting RA treatment within a few weeks after delivery.

RA disease activity monitoring should be done with DAS28, SDAI, or CDAI

Disease activity should be assessed and monitored on RA includes signs and symptoms of disease consist of inflammatory pain, swelling, and stiffness, combined with CRP/ ESR values.

Remission can be measured using the Boolean ACR/EULAR criteria or index (SDAI / CDAI)

The Boolean criteria consist of the number of joint tenderness, the number of joint swelling, the CRP value, and the patient's assessment (range 1-10). In Boolean criteria, the remission achieved if the value of all categories is ≤ 1,[27] the total value of SDAI is ≤ 3.3, and CDAI is ≤ 2.8.

Monitoring comorbidities and complications was performed from the beginning of RA was diagnose

RA patients are at high risk of comorbid diseases such as cardiovascular disease, infections, osteoporosis, malignancies and others. Complications can occur due to disease itself or therapy. Complications in RA do not only occur in the articular (joint deformity) but can also affect extra-articular or systemic.

Monitoring of the efficacy and safety of csDMARD or bDMARD therapy should be done regularly and routinely every 1 month in active disease and every 3 months if remission or LDA is achieved

Frequent monitoring should be done for active RA every 1-3 months. If there is no improvement at 3 months after starting therapy or target is not achieve within 6 months, therapy should be reviewed and

adjusted. If disease activity fails to improve by at least 50% within 3 months, the chances of achieving remission or LDA are low.[27]

Prognostic factor of RA assessed by disease activity, including number of joints involved, acute reactant phase and serology, presence of joint erosion, and response to DMARD therapy.

The poor prognosis of RA will result in reduce survival, increase disability and healthcare costs, progression in structural joint damage requiring total arthroplasty. [41]

In cases of arthritis ≥ 3 joints, positive squeeze test, and morning stiffness ≥ 30 minutes or in cases of arthralgia based on the EULAR 2017 recommendations, RA is suspected and referred from a general practitioner to a specialist of internal medicine/ subspecialty rheumatology to confirm the diagnosis and start DMARD therapy

In cases of arthralgia, if found (according to EULAR 2017 recommendations)[42]:

a) New onset of joint complaints (duration <1 year)
b) The location of the complaint at the MCP joint
c) Duration of joint stiffness ≥ 60 minutes
d) The complaints occur more severe in the morning
e) History of RA in the first-degree family
f) Difficulties to clench the fists on the physical examination
g) positive squeeze test at the MCP joint

No	Recommendations	LOE	GOR	LOA
1	Complete History taking and physical examination should be performed in diagnosis of RA	II	B	9.6
2	RA classification criteria according to the ACR / EULAR 2010 should be used to diagnose RA	II	A	9.5
3	Patients with a suspicion of RA need to undergo an RF examination. If the RF is negative. ACPA examination should be performed	II	B	9.5
4	Before starting csDMARD therapy, initial laboratory tests consist of complete blood count, ESR, CRP, liver and kidney function test, screening for hepatitis B & C, and chest X-rays are required.	II	B	9.2
5	Before starting bDMARD or tsDMARD therapy, additional IGRA and tuberculin tests are required for TB screening, as well as HIV testing for those at high risk.	II	B	9.5
6	To assess complications of the disease, additional examinations are required, such as joint X-rays, musculoskeletal ultrasound, BMD, laboratory tests, and other supporting examinations as indicated.	II	B	9.2
7	To assess the side effects of treatment, routine blood tests, liver and kidney function test, and other examination are necessary as indicated	II	B	9.6
8	The goal of RA management is to control disease activity, obtaining remission or at least low disease activity (LDA).	II	A	9.7
9	RA management includes education, medical therapy and rehabilitation / exercises programs.	II	A	9.7
10	Modality and drugs for the treatment of RA must be chosen based on a shared decision-making between the patient and the doctor.	II	A	9.7
11	Education for the patients includes disease progression, diagnosis and treatment plans, benefits and risks of the therapy, complications, and prognosis.	II	A	9.6
12	Therapy with csDMARD should be started immediately after the diagnosis of RA is made, with methotrexate (MTX) as a primary choice. Unless there is contraindication or intolerance with MTX, other csDMARDs can be used including leflunomide, sulfasalazine, chloroquine, hydroxychloroquine, cyclosporine, azathioprine.	I-III	A	9.7
13	DMARD therapy selection is based on disease activity, drug safety and patient factors such as comorbidities and progressive structural damage.	II	B	9,6

14	NSAIDs or low-dose glucocorticoids can be given before starting DMARD therapy. The dose is immediately reduced or stopped when DMARD is effective.	II	B	9.6
15	If the treatment target is not achieved within 3-6 months with the first csDMARD, the second csDMARD can be added as a combination therapy; or bDMARD can be started as a combination therapy or as csDMARD substitution, especially in patients with poor prognostic factors	I	A	9.5
16	If the treatment target is not achieved within 3-6 months with bDMARD, treatment with another bDMARD or tsDMARD should be considered	II	B	9.2
17	In RA patients with persistent remission for 12 months, consider tapering or stopping bDMARD or tsDMARD especially in combination therapy with csDMARD.	II	B	9.2
18	In patients who achieve persistent remission on csDMARD therapy, a gradual tapering could be considered	III	C	9.5
19	Physiotherapy and physical exercise should be done gradually and regularly to increase muscle strength and joint ROM.	II	A	9.5
20	Live vaccines are not allowed to be given to RA patients receiving DMARD therapy	II	B	9.6
21	Vaccinations that are recommended before giving DMARD are influenza, pneumococcus, Herpes zoster, Hepatitis B, and HPV.	II	B	9.0
22	RA patients should be prepared or planned for pregnancy, preferably after achieve low disease activity or remission	IV	D	9.3
23	The drug safety should be evaluated for couple planning to have children, as well as during pregnancy, and lactation	III	C	9.5
24	Disease activity should be evaluated more closely in the postpartum period, because of the increased risk of recurrence	III	C	9.4
25	RA disease activity monitoring should be done with DAS28, SDAI or CDAI	II	B	9.5
26.	Remission can be measured using the Boolean ACR / EULAR criteria or index (SDAI / CDAI)	II	B	9.5
27	Monitoring comorbidities and complications was performed from the beginning of RA was diagnose	III	C	9.6
28	Monitoring of the efficacy and safety of csDMARD or bDMARD therapy should be done regularly and routinely every 1 month in active disease and every 3 months if remission or LDA is achieved	IV	D	9.5
29	Prognostic factor of RA assessed by disease activity, including number of joints involved, acute reactant phase and serology, presence of joint erosion, and response to DMARD therapy.	II	B	9.6
30	In cases of arthritis ≥ 3 joints, positive squeeze test, and morning stiffness ≥ 30 minutes or in cases of arthralgia based on the	III	C	9.5

EULAR 2017 recommendations, RA is suspected and referred from a general practitioner to a specialist of internal medicine/ subspecialty rheumatology to confirm the diagnosis and start DMARD therapy

5. Conclusion

In summary, update of the IRA diagnosis and management recommendations 2021 provides the most recent guideline consist of 30 recommendations that expected to become reference for rheumatologists and other health practitioner in Indonesia. These recommendations made by considering various aspects such as the availability of drugs and supporting facilities, socioeconomic and cultural conditions in Indonesia, as well as the latest research that can be applied to Indonesian population. With this recommendation, we hope that optimal management can be given, also target therapy can be achieved along with new medical drug options in order to provide better management of RA.

6. References

1. Firestein GS, Mcinnes IB. Review Immunopathogenesis of Rheumatoid Arthritis. *Immunity*. 2017;46(2):183–96.
2. Al-saadany HM, Hussein MS, Zaytoun HA. Egyptian Society of Rheumatic Diseases Th-17 cells and serum IL-17 in rheumatoid arthritis patients : Correlation with disease activity and severity. *Egypt Rheumatol*. 2015;1–7.
3. Panagopoulos PK, Lambrou GI. Bone erosions in rheumatoid arthritis : recent developments in pathogenesis and therapeutic implications. 2018;18(3):304–19.
4. Canella AC, O'Dell JR. Traditional DMARDs: Methotrexate, Leflunomide, Sulfasalazine, Hydroxychloroquine, and Combination Therapy. In: Firestein G, Budd R, Gabriel S, editors. *Kelley and Firestein's textbook of rheumatology*. 10th ed. *Philadelphia: Elsevier*; 2017. p. 958–60.
5. Safiri S, Kolahi AA, Hoy D, Smith E, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of rheumatoid arthritis 1990-2017: a systematic analysis of the Global Burden of Disease study 2017. *Ann Rheum Dis*. 2019;78(11):1463–71.
6. Suryana BPP, Hidayat R, Sumariyono, Wibowo RSAK, Hamijoyo L, Rahmadi AR, et al. DMARD treatment and remission rate in patients with rheumatoid arthritis in Indonesia: The Indonesia RA National Registry (in process for publication). *Jakarta*; 2020.
7. Harbour R, Miller J. A New System for Grading Recommendations in Evidence based Guideline. *Br Med J*. 2001;323(3):334–6.
8. Castrejõn I, McCollum L, Tanriover MD, Pincus T. Importance of patient history and physical examination in rheumatoid arthritis compared to other chronic diseases: Results of a physician survey. *Arthritis Care Res*. 2012;64(8):1250–5.
9. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. Arthritis & Rheumatism. 2010;62(9):2569–81.
10. Littlejohn EA, Monrad SU. Early Diagnosis and Treatment of Rheumatoid Arthritis. *Prim Care - Clin Off Pract*. 2018;45(2):237–55.
11. Ingegnoli F, Castelli R, Gualtierotti R. Rheumatoid factors: Clinical applications. *Dis Markers*. 2013;35(6):727–34.
12. Rigby WFC, Lampl K, Low JM, Furst DE. Review of Routine Laboratory Monitoring for Patients with Rheumatoid Arthritis Receiving Biologic or Nonbiologic DMARDs. 2017;
13. Tehlirian C V, Bathon JM. Rheumatoid Arthritis Clinical and Laboratory Manifestations. In: Klippel JH, Stone JH,

Crofford LJ, White PH, editors. *Primer on the Rheumatic Disease*. 13th ed. *Boston: Springer*; 2008.

14. Wasserman AM. Diagnosis and Management of Rheumatoid Arthritis. *Am Fam Physician*. 2011;84(11):1245–52.
15. Pedersen R, Lukina G, Lichauco JJ, Vasilescu RS. Tuberculosis and viral hepatitis infection in Eastern Europe , Asia , and Latin America : impact of tumor necrosis factor- α inhibitors in clinical practice. 2018;1–9.
16. Mehta B, Zapantis E, Petryna O, Efthimiou P. Screening Optimization of Latent Tuberculosis Infection in Rheumatoid Arthritis Patients. *Arthritis*. 2015;2015:1–8.
17. Perhimpunan Reumatologi Indonesia. Pedoman Penapisan dan Tata Laksana Infeksi Tuberkulosis Laten pada Pasien Reumatik yang Akan Mendapatkan Terapi DMARD Biologik. 2017.
18. Lau CS, Chia F, Dans L, Harrison A, Hsieh TY, Jain R, et al. 2018 update of the APLAR recommendations for treatment of rheumatoid arthritis. *Int J Rheum Dis*. 2019;22(3):357–75.
19. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: Results of an international, cross-sectional study (COMORA). *Ann Rheum Dis*. 2014;73(1):62–8.
20. Klodzinksi L, Wislowska M. Comorbidities in rheumatic arthritis. *Reumatologia*. 2018;56(4):228–33.
21. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: Recommendations of an international task force. *Ann Rheum Dis*. 2010;69(4):631–7.
22. Senara S, Wahed WA, Mabrouk S. Importance of patient education in management of patients with rheumatoid arthritis: an intervention study. *Egypt Rheumatol Rehabil*. 2019;46(1):42.
23. Bakker MF, Jacobs JWG, Welsing PMJ, Vreugdenhil SA, Van Booma-Frankfort C, Linn-Rasker SP, et al. Early clinical response to treatment predicts 5-year outcome in RA patients: Follow-up results from the CAMERA study. *Ann Rheum Dis*. 2011;70(6):1099–103.
24. Cannella AC, O'Dell JR. Traditional DMARDs: Methotrexate, Leflunomide, Sulfasalazine, Hydroxychloroquin, and Combination Therapies. In: Firestein GS, Budd RC, Gabriel SE, Koretzky GA, McInnes IB, O'Dell JR, editors. *Firestein & Kelley's Textbook of Rheumatology*. 11th ed. *Philadelphia: Elsevier*; 2020.
25. O'Dell JR. Treatment of Rheumatoid Arthritis. In: Firestein GS, Budd RC, Gabriel SE, Koretzky GA, McInnes IB, O'Dell JR, editors. *Firestein & Kelley's Textbook of Rheumatology*. 11th ed. *Philadelphia*; 2020.
26. Katchamart W, Trudeau J, Phumethum V, Bombardier C. Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: A systematic review and meta-analysis. *Ann Rheum Dis*. 2009;68(7):1105–12.
27. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79(6):685–99.
28. 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(9410):675–81.
29. Radner H, Smolen JS, Aletaha D. Comorbidity

affects all domains of physical function and quality of life in patients with rheumatoid arthritis. *Rheumatology*. 2011;50(2):381–8.

30. Buckley F, Finckh A, Huizinga TWJ, Dejonckheere F, Jansen JP. Comparative efficacy of novel DMARDs as monotherapy and in combination with methotrexate in rheumatoid arthritis patients with inadequate response to conventional DMARDs: A network meta-analysis. *J Manag Care Pharm*. 2015;21(5):409–23.
31. Fleischmann R, Vencovsky J, Van Vollenhoven RF, Borenstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: The FAST4WARD study. *Ann Rheum Dis*. 2009;68(6):805–11.
32. Edwards JCW, Szczepański L, Szechiński 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(25):2572–81.
33. Teitsma XM, Marijnissen AKA, Bijlsma JWJ, Lafeber FPJ, Jacobs JWG. Tocilizumab as monotherapy or combination therapy for treating active rheumatoid arthritis: A meta-analysis of efficacy and safety reported in randomized controlled trials. *Arthritis Res Ther [Internet]*. 2016;18(1). Available from: http://dx.doi.org/10.1186/s13075-016-1108-9
34. Kuijper TM, Lamers-Karnebeek FBG, Jacobs JWG, Hazes JMW, Luime JJ. Flare rate in patients with rheumatoid arthritis in low disease activity or remission when tapering or stopping synthetic or biologic DMARD: A systematic review. *J Rheumatol*. 2015;42(11):2012–22.
35. Verhoeven F, Tordi N, Prati C, Demougeot C, Mougin F, Wendling D. Physical activity and rheumatoid arthritis. *Rev du Rhum (Edition Fr [Internet]*. 2016;83(2):99–104. Available from: http://dx.doi.org/10.1016/j.jbspin.2015.10.002
36. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol*. 2016;68(1):1–26.
37. Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, Van Assen S, Bijl M, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis*. 2020;79(1):39–52.
38. Østensen M. Contraception and pregnancy counselling in rheumatoid arthritis. *Curr Opin Rheumatol*. 2014;26(3):302–7.
39. Krause ML, Makol A. Management of rheumatoid arthritis during pregnancy: Challenges and solutions. *Open Access Rheumatol Res Rev*. 2016;8:23–36.
40. Swain S, Jena P. Current understanding of rheumatoid arthritis therapy in pregnancy. *Int J Reprod Contraception, Obstet Gynecol*. 2016;5(10):3275–9.
41. Erickson AR, Cannella AC, Mikuls TR. Clinical Features of Rheumatoid Arthritis. In: Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, editors. *Kelley & Firestein's Textbook of Rheumatology*. 10th ed. *Philadelphia: Elsevier*; 2017.
42. Van Steenbergen HW, Aletaha D, Beaart-Van De Voorde LJJ, Brouwer E, Codreanu C, Combe B, et al. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. *Ann Rheum Dis*. 2017;76(3):491–6.