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Overview of Rheumatoid Arthritis therapy: Management options in Indonesia

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ABSTRACT

Rheumatoid arthritis (RA) is chronic disease characterized by inflammation of the synovium, affecting small joints and many other tissues. RA patients experienced loss of functionality, reduced quality of life, and increased morbidity and mortality. The prompt treatment is very important to alleviate sign and symptoms, reduce disability, increase quality of life and halt the progression of joint damage. Pathogenesis of rheumatoid arthritis involves complex interaction of host immunity, environmental factors and genetic predisposition. Treatment strategy for RA has changed over the past 20 years. Traditional approach as administration of non-steroidal anti-inflammatory drugs (NSAIDs) for acute disease had been abandoned. Current strategy includes administration of disease-modifying antirheumatic drugs (DMARDs) as first line therapy. "Treat to target" approach in RA management is directed to achieve clinical remission or at least low-disease activity for RA patients. Unfortunately, many factors are limiting DMARDs therapy for RA patients in Indonesia. Methotrexate should be first line treatment for patients with RA who have access to this agent. Patients who can afford biologic DMARDs could benefit from these agents. However, biologic agents are reported to increased risk of infections, including opportunistic infections. For an endemic country as Indonesia, administration of biologic agents requires a careful observations and screening. In Indonesia, conventional DMARDs as chloroquine and glucocorticoids are the most accessible and cheapest for patients and primary health provider as general practitioners. Hence, for patients that do not have access to rheumatologists and internists, these drugs could be an option.

Kata kunci: rheumatoid arthritis, DMARDs, biologics

INTRODUCTION

Rheumatoid arthritis (RA) is chronic disease characterized by inflammation of the synovium, affecting small joints and many other tissues.[1,2] Patients suffer from chronic pain, loss of joint function and disability[1]. RA patients also experienced loss of functionality, reduced quality of life, and increased morbidity and mortality[3]. The prompt treatment is very important to alleviate sign and symptoms, reduce disability, increase quality of life and halt the progression of joint damage. It is wise to consider the personalized treatment according to the patient's characteristics (including disease activity, comorbidities and features of poor prognosis)[4] and economic burden, especially in low- to middle-income country as Indonesia.

Rheumatoid arthritis includes local processes (as synovial inflammation, cartilage and bone destruction) and systemic consequences (effect to organs

as cardiovascular, liver, brain, lung, glands, muscles and bones). Synovial inflammation leads to hyperplasia, neo-angiogenesis, and pannus development. Chronic synovial inflammation ultimately causes cartilage damage and bone erosion. Furthermore, patients with RA are also jeopardized by increased risks of cardiovascular diseases (as myocardial infarction, stroke, and heart failure), reduced cognitive function, anemia of chronic disease, sarcopenia, osteoporosis, and so on. Risk of malignancies as lymphoma and lung cancer also increased in RA patients.[5] These consequences reduce the quality of life and increase the morbidity and mortality in RA patients.

EPIDEMIOLOGY

Rheumatoid arthritis affects millions of people worldwide. In 2010, RA was affecting 0,24% people globally, females two times more often than males. Prevalence of RA varies from 0,16% (in Asian and North Africa and Middle East) to 0.46% (in Australasia region). The prevalence is highest in Australasia, Western Europe and north America.[6] In low- and middle-income countries, RA affected more than 18 million individuals, females five times more than males. Every year, 4 million of new cases are diagnosed[7]. In Indonesia prevalence varies from 0,3%-0,6% in different areas. New cases of RA reported as 4,1%-9% from all new cases.[8]

PATHOGENESIS

Pathogenesis of rheumatoid arthritis involves complex interaction of host immunity, environmental factors and genetic predisposition.[5] Adaptive and innate immunity play a central role in early pathogenesis. Autoantigens (as type II collagen, proteoglycans, aggrecan, cartilage link protein, heat shock protein) are presented by dendritic cells to naïve CD4 T cells. Activation of T cell requires co-stimulation by CD80 or CD86 through interaction with CD28. Autoreactive CD4 T cells (Th1 or Th17 cells) produce inflammatory cytokines (as TNFα, IL-1, IL-6, IL-17 and IFNγ) or chemokines (chemokine (C-X-C motif) ligand 8 (CXCL8), chemokine (C-C motif) ligand 2 (CCL2)) and matrix metalloproteinases which are responsible for tissue destruction. Autoreactive CD4 T cells also activate B cells, dendritic cells and macrophages. B cells produce antibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA). Macrophages are involved in development of synovitis by release of cytokines, oxygen and nitrogen intermediates, production of prostanoids

and matrix degrading enzymes. Macrophages also have roles in phagocytosis and antigen presentation.[1,5]

Interactions between genetic and environmental factors have been linked to RA. Individuals with certain genotypes (as Human leukocyte antigen (HLA)-DRB1) are associated with positive RF or ACPA.[5] Other genotypes related to RA include polymorphisms in genes encoding for protein tyrosine phosphatase, non-receptor type 22 (PTPN22), cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and signal transducer and activator of transcription 4 (STAT4).[9] Exposure to smoking and other forms of bronchial stress in individuals with HLA-DRB1 and HLA-DR4 has been associated with increased risk of RA. Infections (by Epstein-Barr virus, cytomegalovirus, *Proteus* spp, *E. coli*), periodontal disease (*Porphyro-monas gingivalis*) and gut microbiome also have been linked to development of RA.[5]

DIAGNOSIS

Currently, diagnosis of RA is based on the new 2010 classification criteria by American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) (Table 1). These criteria were developed to identify RA patients as early as possible. Identification of patients with early RA and starting intervention in early disease is intended for the benefit of patients, as therapy are expected to prevent structural damage. Definite RA is indicated if the patient has a score ≥6.[10]

TATATALAKSANA

Treatment strategy for RA has changed over the past 20 years. Traditional approach as administration of non-steroidal anti-inflammatory drugs (NSAIDs) as the first management for acute disease had been abandoned. Current strategy includes administration of disease-modifying antirheumatic drugs (DMARDs) as first line therapy.[11] DMARDs are classified as synthetic chemical compounds (sDMARDs) and biological agents (bDMARDs). Synthetic DMARDs includes conventional DMARDs (methotrexate, sulfasalazine, leflunomide, cyclosporine, minocycline, glucocorticoids, hydroxychloroquine and chloroquine) and targeted synthetic DMARDs (tofacitinib). Biologic DMARDs are anti-tumor necrosis factor (TNF) (infliximab, adalimumab, etanercept, golimumab and certolizumab pegol), non-TNF (abatacept, rituximab, tocilizumab, anakinra) and biosimiliars.[12]

Tabel 1. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis[11]

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥ 6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)#	2
4-10 small joints (with or without involvement of large joints)	3
≥10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

† Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡ Although patients with a score of 6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

§ Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

¶ "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

†† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA=anti-citrullinated protein antibody.

‡‡ Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

§§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status

Conventional DMARDs

Methotrexate (MTX) has become an "anchor drug" for therapy of rheumatoid arthritis, used as first line agent for RA therapy. MTX inhibits amino-imidazolecarboxamide ribonucleotide (AICAR) transformylase and thymidylate synthetase, leads to accumulation of adenosine monophosphate (AMP) in the cell. Outside the cell AMP is converted to

adenosine, which inhibits inflammation.[13] Thus, it suppresses immune cells function, proliferation and inhibits proinflammatory cytokines. Most common adverse effects of MTX are nausea, mucosal ulcers and dose-related hepatotoxicity.[14]

Hydroxychloroquine and Chloroquine are used as antimalarial agents. Mechanism of actions related to RA is proposed by T cell suppression, inhibition of lymphocyte chemotaxis, stabilization of lysosomal enzymes, inhibition of RNA and DNA synthesis and binding of free radicals. Adverse effects include ocular toxicity in high dose (>250 mg/day chloroquine and > 6.4mg/kg/day hydroxychloroquine), dyspepsia, nausea, vomiting, abdominal pain, rashes and nightmares. These drugs are safe in pregnancy.[14]

Leflunomide inhibits T cell proliferation and antibody production by B cells. Adverse effects of leflunomide includes diarrhea (25%), elevation of liver enzymes, mild alopecia, weight gain, increased blood pressure, leukopenia and thrombocytopenia (rare).[14] Sulfasalazine and its active metabolites inhibit inflammatory cytokines production by monocytes and macrophages, suppress T-cell responses and inhibits B-cell proliferation. Adverse effects of sulfasalazine include nausea, vomiting, headache and rash.[14] Cyclosporine, a peptide antibiotic, conveys its action by regulating gene transcription, inhibiting IL-1 and IL-2 receptors, macrophage and T cell interaction and suppressing T cell responses. Adverse effects of cyclosporine are leukopenia, thrombocytopenia, anemia.[14]

Glucocorticoids confer their anti-inflammatory properties by influencing function of transcription factors, as nuclear factor kappa-B (NF-κB). This effect contributes to suppression of proinflammatory cytokines, chemokines and other inflammatory mediators. Glucocorticoids also affect concentration, distribution and function of peripheral leukocytes. Adverse effects of glucocorticoids are related to their metabolic, physiologic and anti-inflammatory and immunosuppressive properties. Low dose of glucocorticoids (equivalent to < 7,5 mg prednisone per day) are reported to be safe. Adverse effects related to low dose glucocorticoid use is cataract, thus ophthalmologic monitoring is recommended for patients receiving the drug.[16] Effects of glucocorticoid administration to RA patients are rapid and dramatic. They are able to slow bone erosions and can be given for serious extra-articular manifestation as pericarditis. Intra-

articular injection is helpful to relieve sign and symptoms in active synovial inflammation. New delayed-release formulation is developed to alleviate symptoms of RA in the morning, according to the circadian rhythm of natural glucocorticoid hormone release.[15,16,17]

Targeted synthetic DMARD

Tofacitinib, a small molecule targeting Janus kinase (JAK) family, mainly JAK3 and JAK1, inhibits JAK-STAT signaling pathway. This pathway has a major role in autoimmune disease, by influencing transcription of genes for differentiation, proliferation and function of immune cells, as T cell, B cell and NK cell. Tofacitinib is given orally with high bioavailability (74%). Adverse effects of tofacitinib includes slight increased risk of infection, such as upper respiratory tract and urinary tract infection (most common), pneumonia, cellulitis, candidiasis and other opportunistic infections (tuberculosis).[9,14]

Biologic DMARDs

Anti-TNF

Anti-TNF drugs for the treatment of rheumatoid arthritis include infliximab, adalimumab, etanercept, golimumab and certolizumab pegol. All anti-TNF agents reported to have similar efficacy and safety.[18,19] Long-term therapy is well tolerated, but the toxicities of anti-TNF should be monitored carefully. Adverse effects of anti-TNF includes increased risk of infections, reactivation of opportunistic infection (as tuberculosis, hepatitis B virus, herpes zoster, candidiasis), increased risk for melanoma and cardiovascular disease.[20] Recent Cochrane review reported that the risk of infections, cancer or death by golimumab was no higher than placebo in short-duration studies. However, the risks in long-term use should be further confirmed by more post-surveillance studies.[21] Certolizumab pegol reported to show rapid effect and to be safe in pregnancy.[22] Anti-drug antibodies could account for failure to anti-TNF therapy and increase the adverse effects.[23]

Non-TNF

Abatacept, a soluble recombinant human CTL4-Ig fusion protein, blocks T cell activation by selectively binds to CD80 or CD86 on the antigen presenting cells, thus inhibits the binding to CD28. It interferes production of TNF, IL-1, IL-6 and B-cell activation. Adverse effects of abatacept include increased risk of infection, infusion and hypersensitivity reactions.[14,24,25,26]

Rituximab, a chimeric monoclonal antibody targeting CD20 molecules on the surface of B cells, depletes mature

peripheral B cells, B cells precursors and memory B cells. Hence, it decreases antigen presentation to T cells, inhibits proinflammatory cytokines production. Adverse effects of rituximab include rash (30%), urticarial, anaphylactoid reaction, (bacterial, viral, fungal) infections, reactivation of hepatitis B virus infection. [14,25-7]

Tocilizumab, a recombinant humanized anti-IL-6 receptor monoclonal antibody, binds to soluble and membrane-bound Il-r receptors and inhibit the IL-6 signaling. Recent meta-analysis reported that tocolizumab monotherapy or in combination with MTX has higher efficacy than anti-TNF or tofacitinib.[28] Serious infection caused by M. tuberculosis, fungi and virus and other opportunistic infections have been reported. Other common adverse effects are headache, hypertension and elevated liver enzymes. [14,25,29]

Anakinra, a recombinant IL-1 receptor antagonist, acts as a competitive inhibitor of proinflammatory IL-1α and IL-1β, decreasing the immune responses. Administration of anakinra is not recommended anymore for RA, since the efficacy is lower than other biologics.[14,26]

Many other new drugs are under clinical trials for RA therapy. These drugs are directed towards new targets. They are expected to be developed with higher efficacy and better safety for certain percentage of patients that do not achieve remission with the current drugs.

Current Recommendation

American College of Rheumatology Recommendations 2012[4]

According to 2012 American College of Rheumatology recommendations for rheumatoid arthritis, there are 5 DMARDs: hydroxychloroquine, leflunomide, methotrexate (MTX), minocycline, sulfasalazine and 8 biologic agents: non-TNF (abatacept, rituximab, tocilizumab) and anti-TNF (adalimumab, etanercept, infliximab, certolimumab pegol and golimumab) recommended for treatment options of RA. Combination of DMARDs consists of 2 drugs, generally methotrexate-based (MTX + hydroxy-chloroquine, MTX + leflunomide, MTX + sulfasalazine, sulfasalazine + hydroxy-chloroquine) or triple therapy (MTX + hydroxychloroquine + sulfasalazine). DMARDs as cyclosporine, azathioprine and gold are excluded from the recommendations due to infrequent use and lack of relevant new data. Biologic agent anakinra is also excluded for the same reason.

European League against Rheumatism recommendations 2013[12]

EULAR also recommends to start DMARDs as soon as possible and aim to reach remission or low disease activity. Algorithm of RA management are divided in 3 phases with follow-up every 1-3 month and evaluation every 6 months to decide whether a new drug needs to be added or changed. Patients with MTX contraindications or those who do not tolerate MTX could be given leflunomide or sulfasalazine. Initial treatment strategy includes low-dose glucocorticoid for up to six months (tapered as rapidly as possible) combined with one or more conventional synthetic DMARDs. Patients that response poorly to conventional DMARDs (with or without glucocorticoids) are recommended to receive biologic DMARDs in combination with MTX. Change to biologic DMARDs should be considered if target is not achieved. Tofacitinib may be considered when all biologics fail to demonstrate good response. Patients with long-term sustained remission are considered to get reduced DMARDs dose with cautions of relapse.[30]

DISCUSSION

ACR/EULAR has recommended "treat to target" approach in RA management in 2010 (updated in 2014). The treatment target is to achieve clinical remission[31] or at least low-disease activity[32] for RA patients. Drug therapy should be evaluated every three months until target is achieved. These principles do not include type of drugs and intervention, the aim was to convey the best outcomes for RA patients.[32-4] This recommendation is made based on the fact that many of RA patients are insufficiently managed. Thus outcomes in delay joint destruction and improvement functional abilities are still suboptimal. To achieve this target, consideration should be given for comorbidities, drug-related risks, financial costs, patient factors and involvement in decision-making.[8] Management of RA patients in Indonesia should also be directed to this "treat to target" approach with all the considerations.

Rheumatoid Arthritis Treatment in Indonesia

In Indonesia, incidence and prevalence of RA is increasing in recent years.[35,36] This increase might be due to increase in life expectancy, improved diagnosis and report of disease. Proper management should be able to improve outcomes for RA patients in Indonesia. DMARDs therapy is expected to modify disease progression by interfering with inflammation, preventing cartilage and bone destruction, thus prevent disability

and improve the overall long-term outcomes in RA patients.[35] Unfortunately, many factors are limiting DMARDs therapy for RA patients in Indonesia, as socioeconomic factors, limited access to health provider and facilities (as clinics and hospital), availability of drugs and lack of support from family and government. Biologic agents as anti-TNF are very expensive for patients and these drugs are not covered by health insurance in Indonesia. Many patients also do not have health insurance, and government's clinic do not provide these drugs. Access to rheumatologist or internist who can give prescription for these patients are only can be obtained by patients living in big cities, while the patients in remote areas do not have access to these specialists.

Availability of DMARDs in Indonesia is one of the limiting factors to prescribe these drugs. Synthetic DMARDs such as MTX, sulfasalazine, leflunomide, chloroquine and cyclosporine are available in Indonesia, but hydroxychloroquine is not available. Biologic DMARDs such as etanercept, infliximab, golimumab, rituximab and tocilizumab can be prescribed by specialists. However, adalimumab, certolizumab pegol, abatacept, anakinra and tofacitinib are yet not available in Indonesia.[8]

MTX should be first line treatment for patients with RA who have access to this agent. MTX has been proved to be efficacious as monotherapy and in combination with other conventional DMARDs or biologic DMARDs.[35] MTX also has been proposed to have protective effect against ischemic cardiovascular disease in RA patients treated with this drug.[37] Adverse effects of MTX could be minimized by co-administration of folic acid.[13,38] Patients that do not tolerate MTX or contraindicated with MTX could be given leflunomide or sulfasalazine, since they are considered similarly effective as MTX. Combination of MTX with glucocorticoids or leflunomide or sulfasalazine could be considered in patients who fail to achieve target, with attention of adverse effects. Patients who can afford biologic DMARDs could benefit from these agents when conventional DMARDs do not give a good response.[39] The treatment strategy to switch between conventional DMARDs and biologics should be done according to recommendations given by ACR or EULAR.[4,12] When biologic DMARDs are not affordable, combination of two or more conventional DMARDs could be a wise decision, since the efficacy of this

combination is not inferior compared to combination of MTX and biologic DMARDs.[40,41]

Biologic agents are reported to increased risk of infections, including opportunistic infections. For an endemic country as Indonesia for tuberculosis, this would be a limiting factor to administer these drugs, since patients are continually exposed to tuberculosis in the general population. Moreover, the incidence of infectious disease in Indonesia is still very high, for instance upper respiratory tract infections account for 40-60% of all visit in government's clinics and 15-30% of all visit in hospital.[42] Therefore, administration of biologic agents requires a careful observations and screening.

In Indonesia, conventional DMARDs as chloroquine and glucocorticoids are the most accessible (and cheapest) for patients and primary health provider as general practitioners. Hence, for patients that do not have access to rheumatologists and internists, who could prescribe MTX as the first line DMARD for RA patients, these drugs could be an option. Chloroquine is not frequently used for RA treatment because of low efficacy and side effect. However, serious adverse effect as ocular toxicity are reported in high dose (>200 mg/day) and rarely occur in dose given for RA (150mg/day).[14] This drug is also considerably safe for long term use. Efficacy of chloroquine could be optimized by combination with low dose glucocorticoid at initial phase. Glucocorticoids use is not recommended by ACR and preferably avoided by many physicians for the reason of the adverse effects for long term use. However, recent review by Santiago et al argued that low dose glucocorticoids (<7,5 mg prednisone or equivalent) is safe for RA therapy. They also pointed out the low cost of glucocorticoids and the superiority of glucocorticoid efficacy (in combination with MTX) to rapidly alleviate symptoms of RA and inhibit bone erosions.[16] EULAR also recommended low-dose glucocorticoid administration as part of initial treatment strategy.[12]

In the future, when biologic agents are more accessible and the cost would be lower (for instance with the biosimiliars), administration of biologics for patients who fail to achieve clinical remission or low disease activity in Indonesia should be carefully considered. Anti-TNFs are first line biologics choice, unless there are contraindications. Although all anti-TNF reported to have similar efficacy and safety,[21,26] incidence of side effects such as anti-drug antibodies are lower with etanercept.[11,18] Etanercept also reported to have more favorable overall treatment

withdrawal profiles.[26,39] Recent review reported risk of tuberculosis is significantly lower with Etanecept.[43] Etanercept also could be administered for patients with Hepatitis C infection. Rituximab should be an option for patients with malignancy or history of malignancy.[4] Screening and surveillance for tuberculosis and hepatitis B virus infections should be diligently employed before and during administration of these drugs.[8]

CONCLUSION

Treatment strategy for RA has changed over the past 20 years. Traditional approach as administration of NSAIDs as the first management for acute disease had been abandoned. Current strategy includes administration of DMARDs as first line therapy. ACR/EULAR has recommended "treat to target" approach in RA management to achieve clinical remission or at least low-disease activity for RA patients. The aim of this principles is to convey the best outcomes for RA patients. Management of RA patients in Indonesia should also be directed to this approach. Proper management should be able to improve outcomes for RA patients in Indonesia. Unfortunately, many factors are limiting DMARDs therapy for RA patients in Indonesia, as socioeconomic factors, limited access to health provider and facilities (as clinics and hospital), availability of drugs and lack of support from family and government. MTX should be first line treatment for patients with RA who have access to this agent. Patients who can afford biologic DMARDs could benefit from these agents when conventional DMARDs do not give a good response. Biologic agents are reported to increased risk of infections, including opportunistic infections. For an endemic country as Indonesia, administration of biologic agents requires a careful observations and screening. In Indonesia, conventional DMARDs as chloroquine and glucocorticoids are the most accessible and cheapest for patients and primary health provider as general practitioners. Hence, for patients that do not have access to rheumatologists and internists, who could prescribe MTX as the first line DMARD for RA patients, these drugs could be an option.

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