Guidelines for the Pharmaceutical Management of Rheumatoid Arthritis
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Working party: Eva Baecklund, Helena Forsblad d'Elia, Carl Turesson

Background

Our purpose is to briefly summarize current principles for the pharmaceutical management of rheumatoid arthritis (RA) on the basis of evidence from the literature or, failing that, consensus. From the 2011 guidelines on, the grading of evidence is done according to the GRADE system as high, moderate, low or very low strength of evidence, where high strength of evidence is the highest degree of evidence (see Appendix 1). In cases where a statement does not lead to a clear recommendation, or recommendations are founded on consensus or expert opinion only, no grading of evidence is presented.
The list of references includes key references supporting the grading of evidence but is not a complete list of relevant literature.
The recommendations, wherever applicable, largely agree with international recommendations, above all the 2010 EULAR (the European League Against Rheumatism) recommendations for the management of rheumatoid arthritis with antirheumatic drugs [1-4], the 2008 ACR (American College of Rheumatology) recommendations for the use of non-biological and biological disease-modifying antirheumatic drugs in rheumatoid arthritis [5], and the preliminary version of the national guidelines for the musculoskeletal diseases of the Swedish National Board of Health and Welfare [6]. The grading of evidence is largely based on the work done in connection with the collection of scientific material for the guidelines of the National Board. In those cases, further information on the evidence compiled and the grading of it may be found in the documentation of the National Board [6].
The recommendations are the result of further development of the latest update of the national treatment guidelines of the Swedish Society of Rheumatology, 2010.

The recommendations have been designed to support rheumatologists in the management of patients with rheumatic disease. As always, each individual rheumatologist is responsible for the design of the treatment of her/his own patients, based on her/his own knowledge and experience.

The recommendations are based on treatment deliberations in early RA and in cases of treatment failure or intolerance of the treatment prescribed, and also apply to patients with established RA in those respects. Special aspects may have to be weighed in for patients with established RA, e.g. various complications of the disease and the patient's experience of treatments prescribed earlier. Extra-articular manifestations and comorbidity are aspects of particular importance for the choice of treatment in cases of long standing illness.

Summary

The treatment of patients with RA aims to reduce disease activity – and if possible achieve clinical remission – and prevent joint destruction and a serious long-term development of the disease. New classification criteria have been created to identify patients with short disease duration and high risk of persistent disease. Prognostic factors are very important for the

choice of treatment. Treatment strategies in early RA have undergone great changes with the early introduction of DMARDs, treatment with larger doses of methotrexate than before in patients with an unfavourable prognosis, frequent check-ups, and more immediate changes of dosage and drug in cases of unsatisfactory effect. Treatment with biological drugs has become more prominent, and structured follow-up of effect and safety in registers is important. Structured attempts to discontinue TNF-inhibiting treatment may be considered in cases of early treatment and good persistent effect.

The guidelines include:

1. Definition of basic concepts concerning diagnosis, disease activity, prognostic indicators and treatment goals
2. Strategy for treatment with disease-modifying, anti-rheumatic drugs (DMARDs) and biologics
3. Alternative preparations
4. Special aspects of biological drugs
5. Corticosteroid treatment in early RA
6. Treatment of extra-articular manifestations
7. Follow-up system and principles of treatment evaluation
8. Other guidelines of relevance to pharmaceutical treatment of RA.
9. Appendix 1-4
10. A summary of important parts of the guidelines in two cartoons.

Summary of the most important items added in the 2011 version

There are a number of minor changes in most paragraphs in the guideline document, but the most important changes are as follows:

- Strength of evidence is graded according to the GRADE system, which is in accordance with the guidelines of the National Board of Health and Welfare.
- A new paragraph on the new ACR/EULAR classification criteria has been added to the *Diagnosis* section, and the criteria are listed in Appendix 2.
- In the *Disease activity and severity* section, there is a discussion of activity indices constituting alternatives to DAS28.
- The *Intermediate disease activity* section has been shortened and now includes a more unreserved recommendation to add a TNF inhibitor in most cases of insufficient effect of methotrexate – in accordance with the guidelines of the National Board.
- The *High Disease Activity* section, too, has been shortened, and now includes a more unreserved recommendation of treatment with a TNF inhibitor in combination with methotrexate as first choice in patients with an unfavourable prognosis – this, too, in accordance with the guidelines of the National Board.
- The recommendation from last year to consider certolizumab and golimumab second choices among TNF inhibitors because of insufficient experience of their use outside clinical trials, has been struck out.
- It is now a more unreserved recommendation that abatacept/rituximab/tocilizumab are to be considered first choices among biological drugs if an indication is present but there is an absolute or relative contraindication to treatment with TNF inhibitors.
- The new indication for abatacept is included in the description of this drug.
- A rather extensive discussion of doses and treatment intervals for rituximab, based on recently presented data, has been added.

- The section on the *Treatment and prevention of osteoporosis* has been replaced by a section listing guidelines for the treatment of osteoporosis and other guidelines from the SRF relevant to the pharmaceutical treatment of RA.

1. Definitions

Diagnosis

The difficulties in diagnosing early RA must not be underrated. New ACR/EULAR classification criteria for RA have been published in 2010 [7]. Those criteria focus on factors in patients with early arthritis associated with persistent and erosive disease and have been prepared in order to facilitate a correct and consistent identification of RA in its early stages. The new criteria will promote early initiation of efficient treatment in order to prevent or retard as much as possible the development of chronic, erosive disease.

Documentation to support treatment recommendations for patients who meet the 2010 criteria but not those from 1987[10], is still sparse. There is some evidence that the treatment with methotrexate of patients with early undifferentiated arthritis (some of them meeting the 2010 criteria) may prevent the development of classical RA and radiographic joint destruction, particularly in patients with anti-CCP antibodies (low strength of evidence) [8]. A reduced radiographic progression has also been seen in the treatment with abatacept of early undifferentiated anti-CCP-positive arthritis (low strength of evidence) [9].

Patients with RF and anti-citrulline antibody negative arthritis will more often than before fall outside the criteria for RA. There is at present no basis for specific treatment recommendations for this group of patients.
Essentially all evidence-based treatment referred to in these guidelines concerns patients who have been included in studies after having met the 1987 ACR criteria for RA [10].
For a Swedish translation of the 2010 ACR/EULAR criteria, please se Appendix 2.

Disease activity and degree of severity

As for the concepts of low/intermediate/high activity, this document presupposes that each individual rheumatologist defines the concepts by means of a total appraisal of clinical findings and biochemical variables. These factors may be assessed individually or in an activity index, e.g. EULAR Disease Activity Score, which includes the number of swollen and tender joints, SR or CRP, and the patient's global assessment of disease activity (VAS scale). As regards DAS28 (28-joint index), clinical remission is defined as DAS28<2.6 and low, intermediate and high disease activity as DAS28 <3.2, DAS28 3.2-5.1, and DAS28 >5.1, respectively. It is important, however, that decisions on treatment and change of treatment are only made after a total appraisal of all information available. Activity indices, therefore, are to be seen as support for the clinician in the decision-making process. Still, clinical reality is too complex to allow treatment decisions to be guided strictly by a DAS score. The relationship between DAS28 and inflammation varies between different individuals, and several studies have reported higher DAS28 scores at group level in women than in men in relation to the degree of inflammation. As an alternative to DAS28, other indices may be used, e.g. the Simple Disease Activity Index (SDAI), which is made up of the sum of the number of tender and swollen joints (28-joint index), the patient's and the doctor's global assessment of disease

activity in cm (VAS, 0-10 cm) and CRP (mg/dl) [12]. The SDAI has been validated, is simple to calculate, and correlates strongly with DAS28. The Clinical Disease Activity Index (CDAI), which is also a validated instrument, is a simplification of the SDAI where the CRP has been excluded. The CDAI therefore contains no acute-phase reactants, and one of its advantages is that it may be calculated immediately without a blood test having to be taken first [13]. Absolut values and changes in DAS28, SDAI and CDAI correlate strongly with each other (Appendix 3).
Other important factors that need to be weighed in are different aspects of the degree of severity: presence of extra-articular manifestations, progressive functional disability and progress of radiographic joint damage [14].

Prognostic indicators

Prognostic indicators for progressive joint destruction are the presence of rheumatoid factor and/or anti-CCP antibodies, high ESR or CRP, early presence of radiographic erosions, and the number of swollen joints [15]. Moreover, there are data suggesting that digital quantification of effects on the corticalis of metacarpal bones using digital X-ray radiogrammetry (DXR), measured as bone loss in the hand over one year, can provide additional prognostic information [16-18]. Genetic factors and tissue markers have been shown to be associated with the future development of joint damage. For the time being, however, there is no basis for recommendations for routine genotyping, measurement of cartilage or bone markers, or DXR measurement.
The more numerous the unfavourable prognostic factors presented by the patient, the worse the prognosis, but the difficulty in judging prognosis in an individual patient is still considerable. Examples of patients with early RA and poor prognosis are patients with both verified anti-CCP antibodies/rheumatoid factor and verified radiographic erosions or highly active disease. Patients with fewer prognostic factors may be said to have an intermediate prognosis.
For future functional ability, but also for comorbidity and mortality, the level of functional ability as measured with the Health Assessment Questionnaire (HAQ) has been shown to have prognostic significance. Severe extra-articular manifestations [19,20] and high, persistent disease activity [21] increase the risk of cardiovascular comorbidity and premature death.
In the assessment of RA patients, lifestyle factors which may influence the prognosis should also be taken into account. Screening for risk factors for cardiovascular disease and intervention against them should be performed in accordance with the separate guidelines of the Swedish Society of Rheumatology. Smoking, besides increasing the risk of comorbidity, may reduce the effect of antirheumatic treatment [22,23].

Treatment goals

The goal for the treatment of patients with RA, particularly in its early stages, should be to achieve remission. There are definitions of the concept of remission (cf. below under Follow-up system and Principles of evaluation), but it must be emphasized that both the ACR and the EULAR definitions [11,24] (see Appendix 3) are defective. New joint ACR and EULAR remission criteria are being prepared. Since the earliest versions of these guidelines, the evidence that low disease activity, defined somewhat differently in different studies, is associated with less destruction and a better preserved long-term functional ability has been strengthened. The importance of careful monitoring and adjustments of the therapy to preserve a low disease activity should be emphasized (cf. below). Programmes with frequent check-ups and active treatment, guided by residual disease activity, have been shown to contribute to a better outcome, above all in early RA (low strength of evidence) [25-27].

Follow-up and development

The treatment of RA and similar arthritic diseases is developing rapidly, and there is still considerable uncertainty as to which therapies are best for individual patients, what side effects may be foreseen, and what long-term effects – positive and negative – of different therapies may be expected. Swedish rheumatologists have excellent opportunities to contribute to the creation of knowledge in all these fields by using the follow-up systems run by the Swedish Society of Rheumatology (registers for early arthritis and for the follow-up of effects and side effects of biological therapies). Contributions to those registers are therefore strongly encouraged, and the results of studies building on the follow-up systems are important for the design of the treatment recommendations. The Swedish Society of Rheumatology also contributes to health economic evaluation of biological drugs through a special committee, HERAS.

2. Strategy for treatment with disease modifying anti-rheumatic drugs (DMARDs) and biologics

Not only the choice of preparation is of importance for the outcome, but also follow-up, evaluation and decisions on changes in therapy. Frequent check-ups and active treatment guided by residual disease activity have been shown to contribute to a better outcome for patients with intermediate to high disease activity (low strength of evidence) [25-27].
A survey of treatment strategies in early RA, recommendations in case of incomplete treatment effect, and recommendations in case of methotrexate intolerance are given in two separate flowcharts.

Low disease activity

Since prognostic indicators are not perfect, particularly for the identification of patients with a good prognosis, treatment with DMARDs is recommended for all patients. There are no studies focusing specifically on patients with low disease activity. Methotrexate is a well documented and tested treatment of RA [15], particularly in patients with factors indicating a poor prognosis. The alternatives for patients with low disease activity are anti-malarial drugs or sulfasalazine.The diagnosis should be continuously re-evaluated in this group of patients. Intra-articular steroid injections is an important supplementary treatment.

Intermediate disease activity

- Step 1: Methotrexate in doses increasing to 20-30 mg/week, preferably within an 8-week time span (high strength of evidence) [28-30]. Individual aspects such as age, renal function and comorbidity should be considered in connection with the choice of preparation and target dose. Parenteral administration may be considered when there is insufficient effect, but the scientific evidence is limited (very low strength of evidence) [31]. Treatment with parenteral methotrexate may also be called for in cases of gastrointestinal intolerance. This

suggestion is based on extrapolation from comparisons of peroral and parenteral methotrexate treatment [32,33], as there are no studies focusing specifically on patients who have not tolerated oral methotrexate. Folic acid substitution reduces the risk of side effects (moderate strength of evidence) [34,35]. A common and well documented treatment regimen is folacin 5 mg., 1-2 tablets per week, not on the same day as methotrexate. Evaluation should be performed after 2-3 months with the maximum dose of methotrexate. The treatment should be combined with low-dose corticosteroids (5-7.5mg daily), particularly during the first two years of early RA, unless special circumstances speak against it (moderate to low strength of evidence; cf. special section below). The optimal duration of treatment with low-dose corticosteroids in early RA is unclear at present. Intra-articular steroid injections is an important supplementary treatment.

Step 2a: Addition of a TNF inhibitor (adalimumab, certolizumab, etanercept, golimumab eller infliximab, *listed in alphabetical order without indication of preference*) (high strength of evidence) [36-39]. Documentation is more extensive and indicates greater effect from TNF inhibitors than from combinations of traditional DMARDs in this situation, and an open, randomized study showed that the probability for response in patients with methotrexate failure is lower for added sulfasalazine and hydroxychloroquine than for added infliximab (moderate strength of evidence) [40]. In patients with insufficient effect of methotrexate, a TNF inhibitor also has documented effect on the progress of structural joint damage (moderate strength of evidence) [37], whereas there is no corresponding documentation for combined treatments with traditional DMARDs.
Treatment with abatacept, rituximab or tocilizumab (*listed in alphabetical order without indication of preference)* may be considered in some patients with absolute or relative contraindications to TNF inhibitors, especially patients with moderate heart failure (NYHA class III), demyelinating neuropathy or overlap syndrome with features of SLE, and severe heart failure (NYHA class IV, not rituximab).

In cases of few or no unfavourable prognostic factors, a combination of methotrexate with other DMARDs may be considered [41]. Combined treatment with methotrexate, sulfasalazine and hydroxychloroquine reduces disease activity more efficiently than treatment with one or two of those DMARDs, but documented experience of added treatment in patients with insufficient effect of methotrexate is limited (low strength of evidence) [42]. There is also evidence that addition of cyclosporine A (low strength of evidence) [43], leflunomide (moderate to low strength of evidence) [44] or intramuscular gold (low strength of evidence) [45] has some effect in this situation. Documentation on long-term experience of these combinations is very limited. Other combined treatments that have been tested are methotrexate combined with sulfasalazine [46] or hydroxychloroquine [47]. Evaluate the effect after 3-4 months in all these alternatives.

2b: If methotrexate is not tolerated: consider sulfasalazine, possibly combined with hydroxychloroquine/chloroquine phosphate. Leflunomide is an alternative. Studies of patients with methotrexate intolerance are lacking, and these recommendations are based on studies of sulfasalazine [48] and leflunomide [49] in methotrexate-naïve patients. Evaluation of step 2 after 3-4 months for sulfasalazine (alone or in combinations), after 2-3 months for leflunomide. In cases of intolerance, contraindications to or insufficient effect of these preparations, other DMARD treatment should be considered (cf. Alternative preparations). In cases of intolerance to methotrexate and several unfavourable prognostic factors: consider treatment with TNF inhibitors registered as monotherapy (adalimumab, certolizumab eller

etanercept, *listed in alphabetical order without indication of preference*). Studies targeting patients with methotrexate intolerance specifically are lacking, and these recommendations are based on studies of etanercept [50] and adalimumab [51] in methotrexate-naïve patients, and on a study of certolizumab in monotherapy for patients who have discontinued earlier DMARD treatment (in most cases including methotrexate) due to insufficient effect or intolerance [52]. Treatment with adalimumab, certolizumab or etanercept without concurrent methotrexate should be combined with other DMARD treatment (low strength of evidence) [53].

Step 3:
In cases of insufficient effect of treatment with a TNF inhibitor in accordance with 2a or 2b: consider treatment with abatacept, rituximab or tocilizumab (*listed in alphabetical order without indication of preference)*, cf. below under *Biologics* (moderate strength of evidence) [54-56]. A change to a second TNF inhibitor is an alternative (low strength of evidence) [57-59].
In cases of intolerance to treatment with a TNF inhibitor in accordance with 2a or 2b: first try a different TNF inhibitor (cf. below). Treatment with abatacept, rituximab or tocilizumab is an alternative.

In patients showing insufficient effect of treatment combinations with traditional DMARDs according to 2a or treatment with traditional DMARDs according to 2b or intolerance to such treatment, TNF inhibitors should be considered if there are signs of progressive joint destruction. If not, further treatment attempts with traditional DMARDs in combinations or monotherapy may be considered.

High disease activity

Step 1: Methotrexate in combination with low doses of corticosteroids, as in cases of intermediate disease activity. Combination treatment with methotrexate, sulfasalazine, hydroxychloroquine and low-dose corticosteroids has better effect than sequential monotherapy with sulfasalazine followed by other DMARDs on disease activity and joint destruction (low strengt of evidence) [60,61] and is therefore an alternative for this group of patients. Direct comparisons between this combination treatment and treatment with methotrexate and low-dose cortisone are lacking.
TNF inhibitors in combination with methotrexate, possibly combined with low-dose corticosteroid treatment as above, are recommended for patients with several factors indicating an unfavourable prognosis (high to moderate strength of evidence) [51,62,63], e.g. patients with verified early radiographic erosions and positive rheumatoid factor or anti-CCP or substantially elevated CRP/SR. The potential advantage of early treatment with TNF inhibitors is greatest in patients with rapidly progressive joint-destructive disease. Direct comparisons in early RA have shown that a combination of a TNF inhibitor and methotrexate is superior to methotrexate alone for patients with high disease activity (high to moderate strength of evidence) [51,62,63]. There is some evidence that combined treatments with methotrexate, sulfasalazine, hydroxychloroquine and high-dose steroids (initially 60 mg prednisolone, rapid reduction) have an effect on disease activity and joint destruction in early RA which may be similar to the effect of the combination of methotrexate and TNF inhibitors [64].

In early initiation of TNF inhibitors it is particularly important that treatment effect and side effects are followed up in a structured manner in national registers, and that discontinuation should be considered in cases of long-term remission (cf. separate sections below).

Step 2:
a) In cases of tolerance but insufficient effect of methotrexate, possibly in combination with low-dose corticosteroid treatment as above, a combination of methotrexate and a TNF inhibitor should be considered (high strength of evidence) [36-39].
Treatment with abatacept, rituximab or tocilizumab (*listed in alphabetical order without indication of preference)* may be considered for certain patients with absolute or relative contraindications to TNF inhibitors, above all patients with moderate heart failure (NYHA class III), demyelinating neuropathy or overlap syndrome with features of SLE, and severe heart failure (NYHA class IV, not rituximab).

b) In cases of intolerance to methotrexate: consider treatment with a TNF inhibitor (adalimumab, certolizumab eller etanercept, *listed in alphabetical order without indication of preference*). Studies targeting patients with methotrexate intolerance specifically are lacking, and these recommendations are based on studies of etanercept [50] and adalimumab [51] in methotrexate-naïve patients, and on a study of certolizumab in monotherapy for patients who have discontinued earlier DMARD treatment (in most cases including methotrexate) due to insufficient effect or intolerance [52]. Treatment with adalimumab, certolizumab or etanercept without concurrent methotrexate should be combined with other DMARD treatment (low strength of evidence) [53].
When there are no prognostically unfavourable factors besides high disease activity, treatment in accordance with item 2b under Intermediate disease activity above is an alternative.

Step 3:
In cases of insufficient effect of treatment with a TNF inhibitor in accordance with 2a or 2b: consider treatment with abatacept, rituximab or tocilizumab (*listed in alphabetical order without indication of preference)*, cf. below under *Biological drugs* (moderate strength of evidence) [54-56]. A change to a second TNF inhibitor is an alternative (low strength of evidence) [57-59].
In cases of intolerance to treatment with a TNF inhibitor in accordance with 2a or 2b: first try a different TNF inhibitor (cf. below). Treatment with abatacept, rituximab or tocilizumab is an alternative.

3. Alternative preparations

Besides the preparations mentioned above, there are a number of other ones which may be useful in particular cases. Cyclosporine A and parenteral gold are registered for use in the treatment of RA and have documented effect on the progression of radiographic joint damage (high strength of evidence) [65], but their use has been restricted by their poor long-term tolerability. Both are well documented in combined treatments (cf. recommendations above). Azathioprine and mycophenolate mophetil have been used in the treatment of RA, but the preparations are not registered for this indication.

4. Special aspects on biological drugs

Choice of TNF inhibitor

Five TNF inhibitors are registered for RA treatment – adalimumab (registered in 2003), certolizumab (registered in 2010), etanercept (registered in 2000), golimumab (registered in 2010), and infliximab (registered in 1999) (*listed in alphabetical order without indication of preference*). Certolizumab and golimumab were registered recently, and long-term experience of their use outside clinical trials is lacking. For certolizumab [66] and golimumab [67] as for the other TNF inhibitors, there is documentation of good effect in patients with earlier insufficient effect of methotrexate (high strength of evidence).

Infliximab and golimumab are registered to be prescribed in combination with methotrexate. Adalimumab and etanercept (*listed in alphabetical order without indication of preference*) may be prescribed as monotherapy, but the effect is better in combination with methotrexate with regard to both reducing inflammation and slowing the destruction of joints (Moderate strength of evidence) [38,39,50]. Certolizumab, too, is registered for monotherapy on the basis of clinical studies [52]. The combination of TNF inhibitors and methotrexate has been shown to be more effective than methotrexate monotherapy in several studies of patients with early, highly active RA (High strength of evidence) [51,62,63].
TNF inhibitors have been used in combination with other DMARDs than methotrexate, including sulfasalazine, leflunomide and azathioprine. Register studies show that long-term effect and tolerability are better in these combinations than in monotherapy with TNF inhibitors [53](low strength of evidence). There is some support for leflunomide combined with TNF inhibitors having effect and tolerability equal to those of the combination of methotrexate and a TNF inhibitor [68,69] (low strength of evidence).
In treatment with TNF inhibitors it should be kept in mind that some patients achieve partial response at three months, and final evaluation can sometimes wait until six months after treatment initiation.
Available data do not indicate that any TNF inhibitor should be more effective than any other [2, 39]. In the choice of preparation, any available experience of individual preparations as well as local resources and costs should be taken into account.
It is not unusual to use infliximab in higher doses than 3 mg/kg or more often than every 8 weeks. Scientific support for higher dosage is limited [70,71]. One randomized, double-blind study showed no difference in outcome between patients who went up to 5 mg/kg and those who remained at 3 mg/kg [72]. There are no randomized, controlled studies which have evaluated the effect of reduced treatment intervals in patients with active disease in spite of standard treatment with infliximab.

Patients with insufficient effect of or intolerance to TNF inhibitors

Randomized placebo-controlled studies have shown that treatment with abatacept (moderate strength of evidence), rituximab (moderate strength of evidence) or tocilizumab (moderate strength of evidence) [54-56] (*listed in alphabetical order without indication of preference*) have effect in patients with inadequate response to TNF inhibitors. Observational studies and clinical experience suggest that treatment with a second TNF inhibitor may also be effective

(low strength of evidence) [57, 58], and this is therefore an alternative treatment strategy. There is further support for this in a randomized controlled study which showed that a recently registered TNF inhibitor, golimumab, had better effect than placebo in patients who had previously been treated with another TNF inhibitor (low strength of evidence) [59].

There is some indication that the effect of rituximab might be better than that of a change of TNF inhibitor (very low strength of evidence) [73]. This emanates from a register study where a benefit from rituximab was only seen in patients who had discontinued an earlier TNF-inhibitor treatment because of insufficient response [73]. Known differences between treatment groups and a risk of selection bias which cannot be measured in the data reported, make it difficult to interpret the comparison [73]. Expanded register studies are expected to yield more information on this, but all such comparisons are rendered difficult by the fact that the selection of patients for different treatments may influence the results. In cases of intolerance to a TNF inhibitor, you can usually change to one of the others (low strength of evidence) [57-59]. Register data suggest that the effect in such cases may be better than that after a change to a different TNF inhibitor following treatment failure [58]. Some caution is advisable after serious side effects.

Abatacept (a human fusion protein which modifies costimulation in antigen presentation and so inhibits T-cell activation) was registered in 2007 (with a change of indication in 2010) ”for the treatment of moderate to severe active RA in adult patients who have had insufficient response from earlier treatment with one or more disease-modifying drugs (DMARDs), including methotrexate or TNF-alpha inhibitors.” The preparation must not be combined with other biological drugs, as the risk of serious side effects, chiefly infections, has then been shown to be raised in patients receiving such treatment [74]. Knowledge of treatment with abatacept after rituximab treatment is limited [75]. There is some support for the view that treatment with a different biologic may start before B-cell levels have been normalised without increased risk of serious infection [76] (very low strength of evidence).
Direct comparisons between different biological drugs with regard to effect and safety are lacking but for one exception. In a randomized study of patients with inadequate response to methotrexate but no earlier biological treatment, the effect of both abatacept and infliximab was better than placebo, but there was no significant difference in treatment response between the two preparations [77].

Rituximab (a chimeric monoclonal antibody against the CD20 antigen on B-lymphocytes) is registered for treatment ”in combination with methotrexate for adult patients with severe active RA who have had inadequate response or are intolerant to other disease-modifying antirheumatic drugs, including treatment with one or more TNF inhibitors.” There is long experience of rituximab from treatment of B-cell lymphoma. The effect of rituximab is best documented from rheumatoid-factor-positive RA patients [78]. Data seem to indicate that the effect of rituximab on a group level is better in RF- and/or anti-CCP antibody positive patients than in antibody negative ones [79].
A dose of 2x500 mg has been studied as an alternative to the recommended 2x1000 mg in patients who have earlier been treated with DMARDs or TNF inhibitors [80,81]. For some clinical outcome measures, but not others, the 2x1000-mg dose comes out significantly better in one of the relevant studies [80], but not in the other one [81]. There are indications that rituximab in the dose of 2x1000 mg (combined with methotrexate) inhibits radiographic progression better than the lower dose (combined with methotrexate). This was studied in a population with early, active RA without previous methotrexate treatment [82].

The duration of residual treatment effect varies between different patients, and the optimal treatment regimen may also vary between patients.For the time being, it is recommended that the need for a new period of treatment shoul be evaluated after 24 weeks and that treatment be repeated at that time if the patient has responded to the treatment but has residual disease activity. In other cases, the patient is monitored and renewed treatment given when there are signs of returning disease activity. For patients who have not responded to treatment after 24 weeks, alternative treatment should be considered.

Available results indicate that a fixed renewal of treatment at 24 weeks may entail better disease control than a symptom controlled renewal of treatment [80]. There is no information on the outcome of other (e.g. individualised) fixed intervals between treatment periods.

Documentation on treatment with rituximab in combination with other DMARDs than methotrexate or with TNF inhibitors is limited. There is, in the form of an abstract, indications that leflunomide works in that situation [83]. There is some support for initiating treatment with a different biologic before B-cell levels have been normalised without raised risk of serious infection [76] (very low strength of evidence).

Tocilizumab (a humanised monoclonal antibody binding to the IL-6 receptor) was registered in 2009 ”in combination with methotrexate for treatment of intermediate to severe RA in adult patients who either have had inadequate effect of or have not tolerated earlier treatment with one or more DMARDs or TNF inhibitors.” According to the registration text, tocilizumab can be prescribed as monotherapy in cases of methotrexate intolerance or when continued methotrexate treatment is inappropriate. Experience of tocilizumab outside clinical trials is limited, so it is recommended primarily as an alternative in cases of treatment failure or intolerance to TNF inhibitors. Tocilizumab is also an alternative when treatment with TNF inhibitors is considered inappropriate. Knowledge is lacking concerning treatment with tocilizumab after treatment with abatacept or rituximab, and concerning combined treatment with tocilizumab and other biologics.

Because of the ability of tocilizumab to inhibit IL-6-mediated activation, acute phase reactants are quickly and efficiently reduced by the treatment. Remission, defined as DAS28<2.6, is reached by more patients, relatively speaking, compared to the proportion of patients who reach remission in terms of disease activity measurements where acute phase reactants have less, (SDAI), or no importance, (CDAI). In comparisons of the effect on disease activity of different biological drugs not all of which have as pronounced an effect on acute phase reactants, this must be borne in mind [84].

Rituximab may be suitable for treatment of patients with earlier B-cell lymphoma [60].

Treatment with abatacept, rituximab [85,86] or tocilizumab (*listed in alphabetical order without indication of preference* may also be considered in some patients with absolute or relative contraindications to TNF inhibitors, particularly patients with moderate cardiac insufficiency (NYHA class III), demyelinating neuropathy or overlap syndrome with features of SLE, and severe cardiac insufficiency (NYHA class IV; abatacept only).

Anakinra

Anakinra is an interleukin-1 receptor antagonist and was registered in 2002 for ”use in combination with methotrexate to treat symptoms in patients with rheumatoid arthritis who

have responded insufficiently to treatment with methotrexate alone". Clinical studies have documented effects with regard to curbing inflammation and slowing destruction (Moderate to high strength of evidence) [87]. Indirect comparisons suggest that the probability for clinical response in patients with insufficient effect of methotrexate is lower for treatment with anakinra and methotrexate than for treatment with TNF inhibitors and methotrexate (low strength of evidence) [39]. Anakinra may be an alternative when TNF inhibitors do not have the intended effect, but there are no studies of the preparation focusing on that particular group of patients. Other, better documented strategies are therefore first-hand recommendations (cf. below).

Inhibition of destruction

Clinical studies show that TNF inhibitors slow the development of joint damage, particularly if the TNF inhibitor is combined with methotrexate (high strength of evidence) [37-39,50]. Effect on tissue damage is an important factor for decisions on therapy but cannot alone guide the clinical decision on the introduction of a preparation or continued treatment. For abatacept as well as rituximab and tocilizumab there are data showing an inhibitory effect on destruction (moderate strength of evidence) [88-90]. For rituximab, an inhibitory effect on destruction has been shown in patients with an inadequate earlier response to TNF inhibitors [89], whereas the data showing an inhibitory effect on destruction for abatacept and tocilizumab are from studies of biologically naïve patients [88,90]. Direct comparisons are lacking, but all in all documentation of inhibitory effects on destruction is better for TNF inhibitors.

A meta-analysis of radiographic progression in clinical trials comprising different DMARDs, steroids and biological drugs reports less radiographic progression in patients treated with DMARD combinations, DMARD combined with cortisone or DMARD combined with a biological drug when compared with treatment with one DMARD preparation [91]. The results show that more extensive treatment on the whole leads to less radiographic progression, but no definite conclusions can be drawn from comparisons between different preparations and combinations. One problem with the analysis is the considerable heterogeneity with regard to comparisons of treatment and effect between different studies, above all as far as traditional DMARDs are concerned. The analysis, therefore, has limited implications for treatment strategies in RA.

Tapering or discontinuation of treatment with TNF inhibitors and other biological drugs

When the patient has been in therapy with a biological drug for some considerable time with a relatively constant, low disease activity, the question will arise whether the drug can be discontinued or the dose reduced. That question is particularly relevant if low disease activity or remission has been achieved for some length of time. There are reports that infliximab may be discontinued with preserved low disease activity [92-94] and some indication that this is also true for adalimumab [95]. This is particularly so if the treatment has been initiated early in the course of the disease and had good and stable effect lingering for several months after discontinuation (low strength of evidence) [92-95]. At present, however, there are no studies on the discontinuation of other TNF inhibitors or tapering of dosage (applies to all TNF inhibitors). So, there is some support for discontinuing treatment with TNF inhibitors in patients with early RA who have achieved remission, provided that a thorough evaluation is performed and readiness to resume treatment is preserved (low strength of evidence) [93].

Current placebo-controlled studies (in progress or planned) are expected to yield more information on the course of events in connection with the discontinuation of treatment with TNF inhibitors or dose reduction in such treatment.

Safety aspects on treatment with biological drugs

The contraindications applying to the preparations must, of course, be observed. For all biological drugs (abatacept, adalimumab, etanercept, infliximab, rituximab and tocilizumab) they include hypersensitivity to constituent substances and active, serious infections. For the TNF inhibitors adalimumab and infliximab, moderate to severe cardiac failure (NYHA class III-IV) is a contraindication, whereas caution is recommended for etanercept in these cases. Severe cardiac failure (NYHA class IV) is a contraindication for rituximab. In treatment with TNF inhibitors, caution is also recommended in cases of demyelinating neuropathy and overlap syndrome with features of systemic lupus erythematosus. For further information on contraindications and recommended caution, please refer to the product monograph in question. As treatment with TNF inhibitors is associated with increased risk of activating latent tuberculosis, the patient should be evaluated in a structured manner with regard to exposure to tuberculosis before treatment with a biological drug, and attentiveness with regard to new exposure to tuberculosis during the treatment period is recommended. For further information and aspects of choice of preparation please refer to "Safety aspects of treatment with DMARDs" (link under 8. below).There are reports of patients with hepatitis B infection who have grown worse and in some cases developed fulminant hepatic failure during treatment with a TNF inhibitor and also during treatment with rituximab against lymphoma, and screening in accordance with international guidelines [86] to detect chronic, active hepatitis B is therefore recommended before the initiation of treatment with TNF inhibitors or rituximab. A meta-analysis showed increased risk of serious infections and malignancies in patients who had been treated with TNF inhibitors in clinical trials [96], whereas observational studies with longer follow-up times do not show any significant increase of risk for these comorbidities [97,98]. A later meta-analysis which included more clinical trials [99], did not indicate any significant increase of risk of serious infections or malignancies in patients who had been treated with TNF inhibitors in the doses recommended. Additional follow-up in registers of patients with RA who are given biological drugs is of great importance for the evaluation of these comorbidities as well as unusual side effects.

5. Corticosteroid treatment in early RA

Prednisolone (5-7.5 mg/day) is recommended, primarily in combination with DMARD, for patients with early RA and intermediate to high disease activity (moderate to low strength of evidence) [4,100-103]. Rapid curbing of the inflammation is often achieved (low strength of evidence) [100], and evidence of retarded joint destruction can be found in studies running over two years (high strength of evidence) [101,103]. A higher initial dose of cortisone tapering off to low dose gives better curbing of disease activity in the high-dose phase [4,100], but the effect on disease development in the long run is unclear. The value of cortisone treatment must be weighed against the risks associated with the treatment. Osteoporosis prophylaxis and treatment should be given in accordance with special treatment guidelines (cf. separate section below).

A possible alternative or complement to oral, low-dose prednisolone treatment are intra-articular corticosteroid injections, whose long term effects and addictive properties are probably smaller than those of peroral treatment. Systematic treatment with intra-articular steroid injections in inflamed joints has been part of treatment programmes which have led to considerable improvement in patients with early RA [25-27], but direct comparisons with treatment programmes without such injections are lacking. Information on the effect of intra-articular corticosteroid injections on joint destruction is lacking.

6. Treatment of extra-articular manifestations

In severe extra-articular manifestations like systemic vasculitis with or without serious ocular complications (scleritis or retinal vasculitis) or vasculitis-associated peripheral neuropathy, treatment with cyclophosphamide and high-dose corticosteroids is recommended according to the same principles as for primary systemic small-vessel vasculitis (low strength of evidence) [104,105]. Such treatment should also be considered for interstitial lung disease with rapidly progressive symptoms (very low strength of evidence) [106]. Treatment with chlorambucil (low strength of evidence) [107] or cyclophosphamide (very low strength of evidence) [107] is recommended for systemic amyloidosis with serious organ effects. There is some support for treatment with TNF inhibitors in this context (very low strength of evidence) [108]. There are reports that TNF inhibitors may have a negative effect on interstitial lung disease [109]. Cyclosporine may be considered in that situation (very low strength of evidence) [110,111]. High-dose corticosteroid treatment can be effective in severe extra-articular manifestations, also in situations where other kinds of immunosuppression are not used [112]. As for the rest, active DMARD treatment is recommended for patients with extra-articular manifestations, both to reduce the risk of further extra-articular complications and to prevent serious developments in other respects [112]. Leucocyte levels in neutropenic patients with Felty's syndrome, for instance, are often improved in connection with treatment with methotrexate or parenteral gold (very low strength of evidence) [113,114].

7. Follow-up system and principles for therapy evaluation

It is essential that individual effect goals are defined, and that the treatment is evaluated continuously. The clinical evaluation includes e.g. HAQ, VAS scales for global health and pain, joint tenderness/swelling, and biochemical markers of inflammation. In clinical practice, DAS levels, CDAI levels or SDAI levels may well be used in evaluations. ACR response criteria and EULAR response criteria can be used in the clinical evaluation of the individual patient, but it should be kept in mind that those measurements were developed primarily for use in clinical trials. Criteria for remission according to ACR or EULAR should also be considered (cf. Appendix 1). Studies on optimal monitoring of radiographic joint destruction are lacking, but in accordance with the EULAR guidelines [15] and routine procedures in the Swedish RA register, it is proposed that hands and feet be X-rayed at diagnosis and at 6-12-month intervals during the first years. Later, too, radiography may be needed as documentation for decisions on the escalation or de-escalation of treatment. In sum, it should be emphasized that no individual measurement of effect can replace the rheumatologist's overall assessment of treatment response.
If the treatment results in a clinically significant improvement after a total appraisal of all the available information mentioned above, it is to be continued; if not, it is to be discontinued. If

the effect is doubtful, a structured attempt at discontinuation is recommended, i.e. an evaluation of disease activity after discontinuation according to the principles outlined for the evaluation of treatment effect. Also cf. *Tapering or discontinuation of treatment with TNF inhibitors and other biological drugs* above.
Follow-up of patients treated with new or established forms of therapy, is to be made in a structured manner to verify treatment effects shown in clinical studies but also, and not least, to monitor the development of side effects. It should be emphasized here that all unexpected incidents during treatment with new preparations are to be registered and reported regardless of whether the incidents are thought to be related to the treatment or not.
All those who treat patients with RA are recommended to follow up effects and side effects of treatment using the RA register run by the Swedish Society of Rheumatology, where a special follow-up of biological treatment is made with the help of the national ARTIS register (through the Southern Sweden Arthritis Treatment Group (SSATG) of south Sweden). It is recommended that side effects should be reported within the framework of the national follow-up system, which includes an electronic report module for side effects for reports directly to the Swedish Medical Products Agency.

8. Other guidelines relevant to the pharmaceutical management of RA

Safety aspects of treatment with DMARDs

Guidelines may be found on the home page of the Swedish Rheumatological Society (http://www.svenskreumatologi.se/index2.htm).

Primary prevention with regard to cardiovascular risk factors in inflammatory rheumatic disease

Patients with RA, seen as a group, run a greater risk of developing cardiovascular disease compared to the general population. This is particularly true of patients who have extra-articular manifestations and/or persistently elevated ESR/CRP. These groups have an elevated risk comparable to that of diabetes mellitus patients. So, it is crucial that rheumatologists screen for cardiovascular risk factors and initiate treatment of them. For reasons to do with local traditions, however, the treatment, in most cases, should be performed by or in close cooperation with the primary health service. But it is our job to spread knowledge about the elevated risk of cardiovascular disease in rheumatics to the primary health service. Please refer to the guidelines on our home page: (http://www.svenskreumatologi.se/index2.htm).

Osteoporosis

Besides reduced peri-articular bone density, patients with RA are also at elevated risk of generalised osteoporosis and osteoporosis-related fractures. Low bone density is associated with the degree of erosiveness, and the loss of bone density is connected with disease activity, among other things [115,116]. In addition to treatment with DMARDs of RA patients, decisions should be taken on the need for investigation, prevention and treatment of osteoporosis. Please refer to the treatment recommendations for osteoporosis of the Swedish Medical Products Agency (http://www.lakemedelsverket.se/upload/halso-och-sjukvard/behandlingsrekommendationer/osteoporos2007.pdf), the EULAR 2007 recommendations for the management of cortisone treatment in rheumatic diseases [117] and the 2010 ACR recommendations for the prevention and treatment of cortisone induced osteoporosis [118]. With the help of the computer-based WHO fracture risk assessement tool (FRAX), the risk of fracture may be assessed. The result is an aid with which to decide

whether bone density measurements should be taken and specific treatment initiated. Having taken 5 mg of prednisolone per day for at least three months and suffering from RA are two of several risk factors in FRAX (http://www.shef.ac.uk/FRAX/?lang=se). The Swedish National Board of Health and Welfare is preparing guidelines for the diagnostics and treatment of osteoporosis [6].

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Appendix 1 – Evidence Grading

Quality grading of evidence according to the GRADE system www.gradeworkinggroup.org

Strength of evidence	Design of study	Downgrade if	Upgrade if
High (++++)	RCT	*Quality of study:* Serious limitations (- 1) Very serious limitations (-2) Obvious heterogeneity (-1) *Generalisability:* Some uncertainty (- 1) Definite uncertainty (-2) Unreliable data (-1) High risk of publication bias (-1)	Strong relationships and no probable confounders (+1) Very strong relationships, no serious threats to validity (+2) Definite dose-response relationship (+1)
Moderate (+++)			
Low (++)	Observational study		
Very low (+)			

RCT: Randomized controlled trial

Appendix 2 –ACR/EULAR classification criteria

2010 ACR/EULAR classification criteria for rheumatoid arthritis

Target population for classification criteria:
Patients with definite clinical synovitis (swelling) in at least 1 joint[1] with the synovitis not better explained by another disease[2]

Classification criteria for RA (score-based algorithm; add the scores for categories A-D. The diagnosis of definitive RA requires a total score of ≥6/10 [3]).

	Score
A. Joint involvement[4]	
1 large joint[5]	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints) [6]	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least one small joint) [7]	5
B. Serology (at least 1 test result is needed for classification) [8]	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acut-phase reactants (at least 1 test result is needed for classification) [9]	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms[10]	
< 6 weeks	0
≥ 6 weeks	1

[1] The criteria are aimed at classification of newly presenting patients.
Other patients to be classified as RA are
1. patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria
2. patients with longstanding disease, including those whose disease is inactive (with or without treatment) who have previously fulfilled the 2010 criteria.

[2] Differential diagnoses may include conditions such as SLE, psoriatic arthritis, and gout. In cases of doubt, an expert rheumatologist should be consulted.

[3] Patients with a score of <6/10 can be reassessed and the criteria might be fulfilled cumulatively over time.

[4] 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 involvement 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.

[5] "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

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

[7] 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 joints).

[8] Negative values refer to values that are less than or equal to the upper limit of normal for the laboratory; low-positive refers to values that are higher than normal but ≤3 times the upper limit of normal; high-positive refers to values that are >3 times the upper limit of normal for the laboratory and assay. When 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, usually measured as anti-CCP.

[9] Normal/abnormal is determined by local laboratory standards.

[10] 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.

Reference: [7]

Appendix 3- Grading of disease activity

- DAS28 ESR: remission < 2.6 ≤ low ≤ 3.2 < intermediate ≤ 5.1 < high
- SDAI: remission ≤ 3.3 < low ≤ 11 < intermediate ≤ 26 < high
- CDAI: remission ≤ 2.8 < low ≤ 10 < intermediate ≤ 22 < high

Ref. [84]

Appendix 4 - Remission Criteria

The remission criteria of EULAR as well as of ACR define patients with no or very low disease activity, but there is no precise limit which defines a good prognosis in the individual patient.

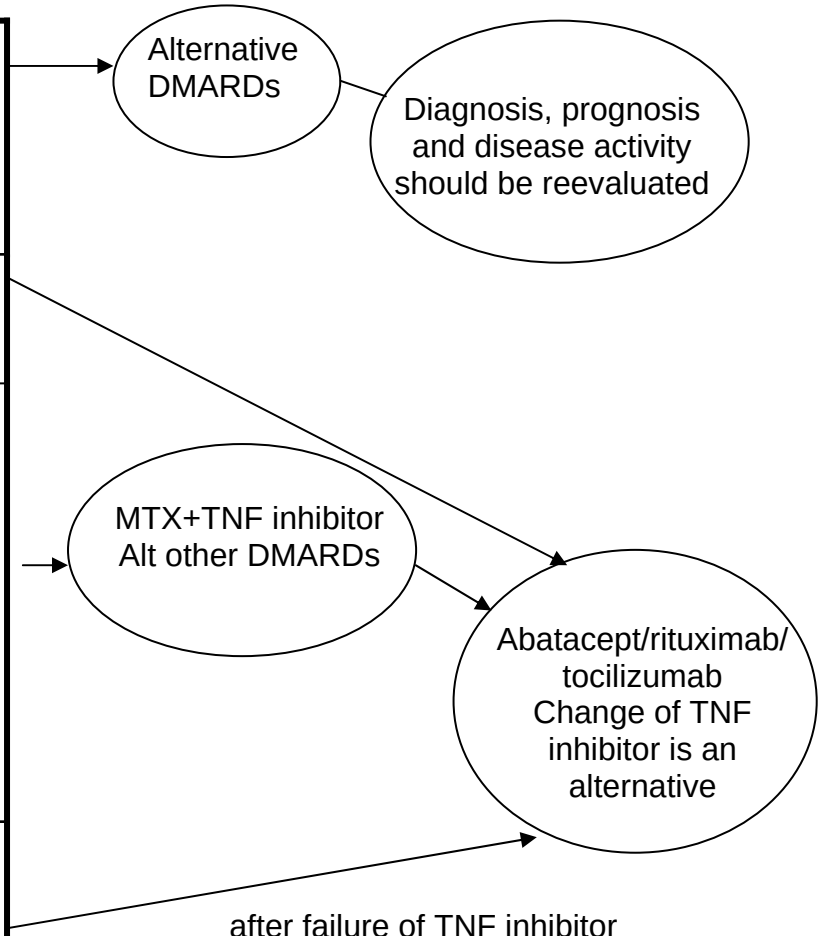
EULAR criterion for remission: DAS28 < 2.6 (9)

ACR criteria for remission [24] (5 out of 6 are to be met for at least two months):

-Morning stiffness < 15 minutes
-No disease-related fatigue
-No joint pain by history
-No joint tenderness or pain on palpation or motion
- No soft-tissue swelling in joints or tender sheats
-ESR < 30 mm/h in women; < 20 mm/h in men.

Treatment strategies in early RA and recommendations in cases of insufficient treatment effect

Low disease activity	Methotrexate (MTX)* Sulfasalazine (SSZ) Anti-malarial drugs (Chloroquin phosphate or hydroxychloroquine (HCQ))	
Moderate disease activity	MTX + low-dose steroids	MTX+TNF inhibitor +low-dose steroids
		If few/no unfavourable prognostic factors: MTX+SSZ+HCQ MTX+Leflunomide MTX+Cyclosporine A and other combinations +low-dose steroids
High disease activity	MTX MTX+SSZ+HCQ MTX+TNF inhibitor** +low-dose steroids	



*above all with factors indicating unfavourable prognosis

**with several factors indicating unfavourable prognosis, e.g. verified early erosions

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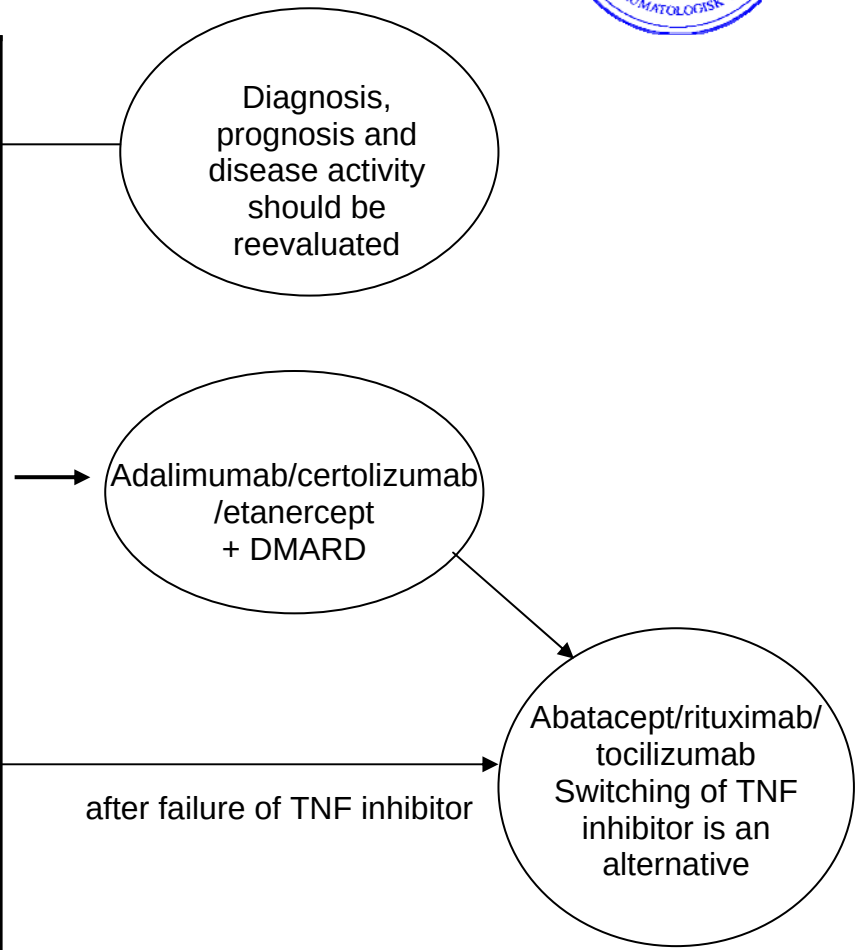
2011-04-14

Pharmaceutical treatment of RA:
Recommendations in cases of intolerance to methotrexate

Low disease activity	Sulfasalazine Anti-malarial drugs (Chloroquin phosphate or hydroxychloroquine) Alternative DMARDs
Moderate disease activity – few unfavourable prognostic factors	Sulfasalazine Leflunomide Alternative DMARDs +low-dose steroids
Moderate disease activity - several unfavourable prognostic factors High disease activity	Adalimumab/certolizumab/ etanercept + DMARD Sulfasalazine Leflunomide Alternative DMARDs +low-dose steroids



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