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Recommendations

Recommendations of the French Society for Rheumatology. TNFα antagonist therapy in rheumatoid arthritis

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Abstract

Objectives: To develop recommendations for TNFα-antagonist therapy in patients with rheumatoid arthritis (RA) seen in everyday practice, under the aegis of the French Society for Rheumatology.

Method: We used the methods recommended by the French Agency for Healthcare Accreditation and Evaluation, the AGREE collaboration, and the European League against Rheumatism (EULAR). The recommendations focus on patient selection, monitoring, and treatment adjustments.

Results: Criteria for selecting patients eligible for TNFα-antagonist treatment of RA include: 1) a definitive diagnosis of RA; 2) disease activity for longer than 1 month, including presence of objective signs of inflammation; or radiographic progression; 3) previous failure of methotrexate in the highest tolerated dosage or of another disease-modifying antirheumatic drug in patients with contraindications to methotrexate; 4) absence of contraindications to TNFα-antagonist therapy. When starting TNFα-antagonist therapy 1) a thorough baseline evaluation should be conducted; 2) any of the three available agents can be used, as no differences in efficacy have been identified in patient populations; 3) concomitant methotrexate therapy is recommended regardless of the TNFα antagonist used; and 4) patients should receive standardized follow-up at regular intervals. Treatment adjustments should be based on the following: 1) the treatment objective is achievement of a EULAR response; 2) when such a response is not achieved, the dosage or dosing interval can be changed, or the patient can be switched to another TNFα antagonist; 3) in patients who experience intolerance to a TNFα antagonist, another TNFα antagonist may be tried, depending on the nature of the adverse event; 4) occurrence of a remission should lead to a reduction in symptomatic medications, most notably glucocorticoids where used; in the event of a prolonged remission, either the TNFα antagonist or the concomitant disease-modifying antirheumatic drug may be reduced.

Conclusion: These recommendations are intended to help physicians use TNFα antagonists in their everyday practice with RA patients. They do not constitute regulations.

Keywords: Rheumatoid arthritis; TNFalpha antagonists; Recommendations; Clinical practice; Treatment; Disease-modifying antirheumatic drugs

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1. Introduction

Radical changes in the management of rheumatoid arthritis (RA) have been introduced in recent years, probably improving both functional outcomes and survival [1]. In parallel with the advent of new drug classes and the development of optimized strategies [2–4], new clinical practice guidelines have been issued in France and in Europe [5–9].

The introduction of TNFα antagonists has proved a breakthrough in RA management. However, TNFα antagonists are costly and can induce serious adverse events, indicating a need for careful risk/benefit assessment and close attention to cost-containment [10–14]. Recommendations for using TNFα antagonists in RA have been issued [15–17] but need to be adapted to practice patterns in France. Recommendations seek to standardize clinical practice, thereby improving healthcare quality and uniformity [18]. In France, physicians are not required to comply with recommendations. When the recommendations seem unsuited to the situation of an individual patient, the physician is free to depart from them, provided the reasons are clearly explained in the medical record.

2. Methods

We used the method suggested by the ANAES for developing clinical practice guidelines (RPC) [19], and we complied with the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria [20]. Three task forces worked on the recommendations under the coordination of a teaching hospital rheumatologist. The literature review task force, composed of three teaching hospital rheumatologists (AC, JM, OV), reviewed the scientific literature on biotherapies for RA. Material published between 1980 and January 2005 was retrieved by searching PubMed and the Cochrane Library and classified according to level of evidence [21]. The literature review task force presented their findings to a panel of experts composed of eight teaching hospital rheumatologists and one clinical epidemiologist. The panel drafted the recommendations during two meetings and a conference telephone call. Finally, the relevance and clarity of the recommendations were validated by a review panel composed of three teaching hospital rheumatologists, four office-based rheumatologists, one rheumatologist from another French-speaking country, four physicians outside the field of rheumatology, a pharmacist specialized in drug surveillance, and a health insurance physician.

The following objectives were selected: to define criteria for identifying RA patients likely to benefit from TNFα antagonist therapy, to define the modalities for initiating TNFα antagonist therapy, and to define treatment adjustments based on the therapeutic response. For each of these objectives, the panel of experts selected three to four questions among a longer list. The recommendations were built around the answers to these questions.

After the recommendations were drafted by the panel of experts and validated by the review panel, the final wording was developed and the strength of each recommendation was determined based on the level of the underlying evidence [21].

3. Results

3.1. Identifying patients likely to benefit from TNFα antagonist therapy

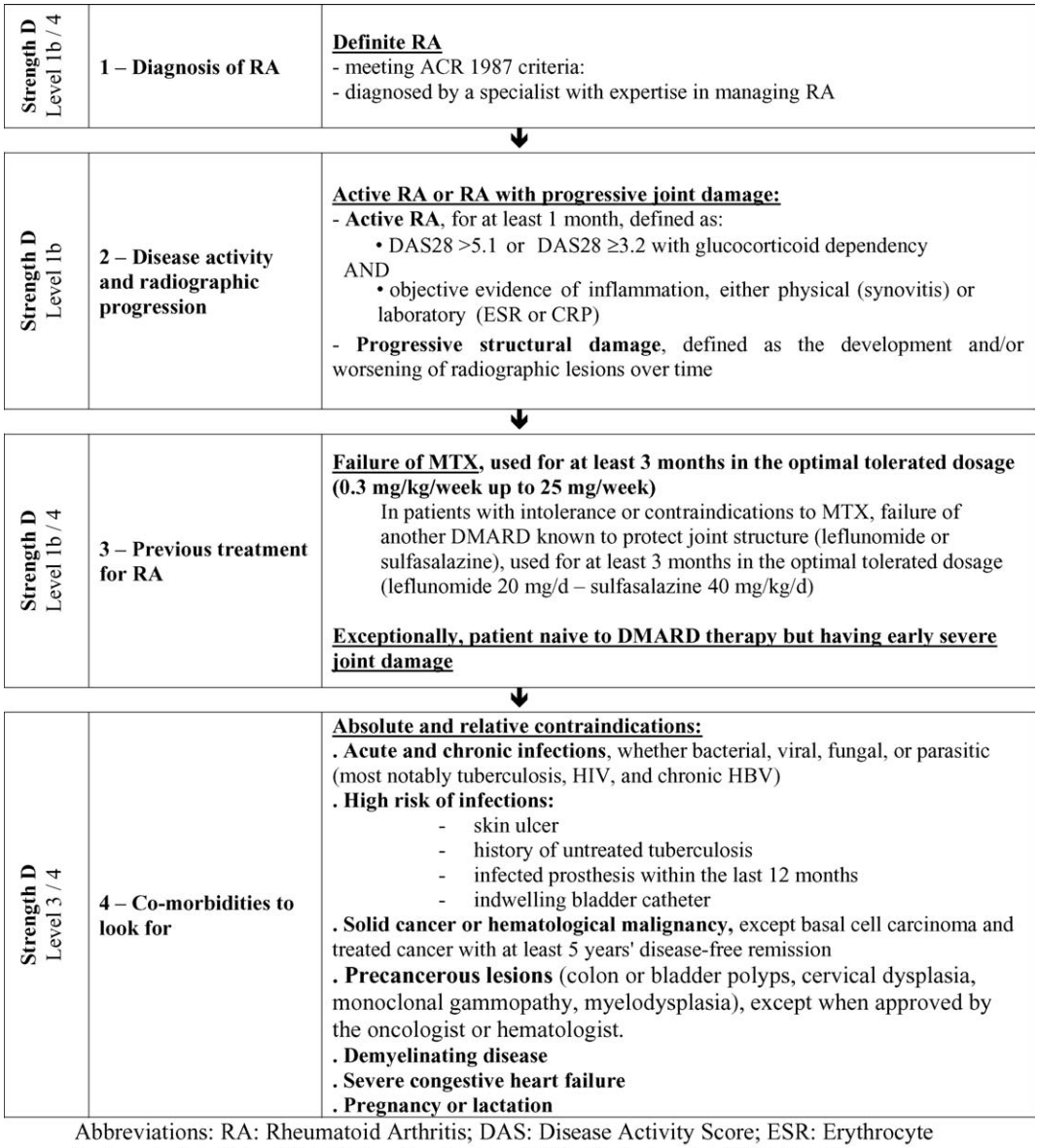
3.1.1. Diagnosis of rheumatoid arthritis

TNFα antagonist therapy can be considered in patients with a definitive diagnosis of RA (Fig. 1, point 1). This opinion is based on findings from controlled therapeutic trials (level 1b) [3,10,11,22–46], the opinion of experts in other countries [15,17,47], the wording in the marketing authorization, and the opinion of the panel of experts convened for drafting the present recommendations (level 4). American College of Rheumatology criteria are the only validated criteria to date and should therefore be used, although they are old and fail to include recently introduced diagnostic criteria such as antibodies to citrullinated cyclic peptide, ultrasonography, and magnetic resonance imaging.

3.1.2. Inflammation activity and structural severity of the disease

TNFα antagonist therapy can be considered in patients with active disease and/or progressive structural joint damage (Fig. 1, point 2). In published trials, active disease was defined as a DAS44 (44 joints) greater than 3.2 [38,41] or as a combination of a swollen joint count > 6, 10, or 12; a tender joint count greater than 6, 9, or 12; and laboratory evidence of inflammation (erythrocyte sedimentation rate > 28 mm/h or C-reactive protein > 15 or 20 mg/L) [3,22–24,26–32,34–36,39,40,44,45,48]. In a few studies, the two clinical criteria were used without the laboratory criterion [25,33,42,43].

In the present recommendations, activity of the inflammatory process is defined based on the DAS28 (28 joints). This score is widely used in everyday practice [6]. Regular DAS28 determination has been reported to improve control of the inflammatory process [49]. DAS28 values greater than 5.1 indicate severe inflammation [50], similar to that in the therapeutic trial populations. However, the panel of experts felt that 3.2 was an appropriate cutoff for patients dependent on glucocorticoid therapy. Many studies have documented adverse effects of glucocorticoid therapy on the bone, skin, blood vessels, and lens, even with dosages smaller than 10 mg/day [51,52]. There is no universally accepted definition of glucocorticoid dependency. Nevertheless, experts agree that the glucocorticoid dosage should not exceed 0.1–0.2 mg/kg/day of prednisone-equivalent. When determining the maximum acceptable dosage in an individual patient, age, cardiovascular risk factors, and other patient characteristics should be taken into consideration. In addition to the DAS28, an objective criterion is needed (e.g. clinical synovitis or laboratory evidence of inflammation). The DAS28 relies on two subjective criteria, namely, the tender joint count and a patient-assessed visual analog scale score for disease activity. These criteria alone



Abbreviations: RA: Rheumatoid Arthritis; DAS: Disease Activity Score; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; MTX: Methotrexate; DMARD: Disease Modifying Anti-Rheumatic Drug; HIV: Human Deficiency Virus; HBV: Hepatitis B Virus.

Fig. 1. Recommendations for selecting patients for TNFα antagonist therapy.

can result in DAS28 scores above the threshold for considering TNFα antagonist therapy [53,54]. Moreover, sustained disease activity is required, as short-lived flares respond to symptomatic therapy. Thus, the present recommendations state that disease activity must be assessed twice at an interval of 1 month, although not necessarily by the same physician.

Radiographic progression has been documented in patients with low levels of disease activity [55–61]. Therefore, the panel selected radiographic progression as a criterion for using TNFα antagonist therapy, independently from the activity of the inflammatory process. The best means of evaluating structural damage due to RA is not agreed on [7]. For the present recommendations, progression was defined as worsening of radiographic abnormalities over a brief period, about 1 year, or up to 3 years in patients with long-standing disease. Worsening may manifest as the development of erosions, the development or worsening of joint space loss, or the development of joint subluxation.

3.1.3. Previous treatments for rheumatoid arthritis

TNFα antagonists have a number of disadvantages, including a potential for inducing serious adverse events (most notably infections), absence of long-term safety data, and high cost. Therefore, they are recommended for patients who fail to respond to, or to tolerate, conventional treatments with documented efficacy on inflammation and radiographic progression: methotrexate (MTX) in the optimal dosage of 0.3 mg/kg/week if tolerated (without exceeding 25 mg/week), leflunomide in a dosage of 20 mg/day, or sulfasalazine in the optimal dosage of 40 mg/kg/day if tolerated (Fig. 1, point 3).

Several trials showed that first-line TNFα antagonist therapy was effective in patients with severe inflammation or early erosions [3,29,34,35,46]. In practice, however, first-line TNFα antagonist therapy is rarely appropriate. Caution should be exercised until more is known about the long-term efficacy and safety of TNFα antagonists (Fig. 1, point 3).

3.1.4. Co-morbidities to look for before starting TNFα antagonist therapy

A list of contraindications to TNFα antagonist therapy was established (Fig. 1, point 4) based on the marketing authorizations; summaries of product characteristics; and post-marketing data collected in France, Europe (EMEA), and the US (FDA). TNFα antagonist therapy may induce exacerbations of chronic hepatitis B virus infection and HIV infection. Safety data in patients with hepatitis C infection are more reassuring. In patients with joint prosthesis infection, TNFα antagonist therapy should not be started within 12 months after removal of the infected material. The risk of reactivation is higher and longer lasting when the prosthesis is left in place. In this situation, the advice of an infectiologist should be sought. In patients with a history of cancer or precancerous lesions, the appropriateness of TNFα antagonist therapy should be discussed with the oncologist or hematologist, and the patient's consent should be obtained after in-depth information about the expected risks and benefits of TNFα antagonist therapy.

3.2. Initiation of TNFα antagonist therapy in patients with rheumatoid arthritis

3.2.1. Pre-treatment evaluation

The pre-treatment evaluation (Fig. 2, point 1) should be conducted as recommended at http://www.cri-net.com/ [62]. Patients who have been in contact with tuberculosis patients should receive prophylactic therapy as recommended by the AFSSAPS (available on the same site). Furthermore, immunizations should be updated if needed.

3.2.2. Selecting the TNFα antagonist

Available TNFα antagonists have not been ranked according to efficacy (Fig. 2, point 2) and have not been compared directly in controlled trials. The only indirect comparison

Strength D Level 3 / 4	**1 – Pre-treatment evaluation**	**Investigations** . Blood cell counts . Serum protein electrophoresis . Transaminases . Serologic tests for HBV, HCV, and HIV (with the patient's consent) . ANA; if significant titer, anti-dsDNA . Chest radiograph . Intradermal tuberculin test (5 Units) . Update immunizations of needed
↓		
Strength C Level 3	**2 – Selecting the TNFα antagonist**	**There is no ranking based on efficacy.** Selection is based on: . the patient's characteristics and preferences . the prescription and delivery modalities . the available safety data.
↓		
Strength D Level 1b /4	**3 – Concomitant medications**	**Concomitant MTX is recommended with all the available TNFα antagonists** When MTX cannot be used, another DMARD should be tried in patients taking adalimumab or infliximab.
↓		
Strength D Level 3 / 4	**4 – Monitoring**	**Monitoring to evaluate the treatment response and to detect side effects should include:** **- Physical examination:** data needed to determine the DAS28. **- Laboratory tests:** ESR, CRP, blood cell counts, transaminases, variables needed to monitor the concomitant DMARD. **- Radiographs:** AP radiographs of the hands and wrists, AP radiographs of the feet, radiographs of symptomatic joints. **Monitoring should be performed**: - at the time of the infusions with infliximab - after 1 month and 3 months then at 3-month intervals with etanercept and adalimumab **Radiographs** should be obtained once a year or at longer intervals in patients with long-standing disease

Fig. 2. Recommendations about initiating TNFα antagonist therapy.

found no difference in efficacy across the three available compounds (infliximab, eternacept, and adalimumab) [63]. Neither have differences in drug continuation rates been reported [64]. Therefore, any of the three compounds can be used first: infliximab (Remicade®) in a starting dosage of 3 mg/kg intravenously at weeks 0, 2, 6, and 14 then every 8 weeks; etanercept (Enbrel®) in a dosage of 25 mg subcutaneously twice a week (although a 50-mg once a week schedule should be available soon); or adalimumab (Humira®) in a starting dosage of 40 mg subcutaneously at 2-week intervals.

3.2.3. Concomitant conventional therapy

Concomitant MTX therapy is recommended with all three TNFα antagonists (Fig. 2, point 3). Combining TNFα antagonist therapy with a conventional disease-modifying antirheumatic drug (DMARD) improves the symptomatic and structural efficacy without compromising the safety profile. Thus, the MTX-infliximab combination was characterized by greater efficacy and a decreased rate of escape phenomenon compared to infliximab alone, possibly as a result of decreased rates of anti-infliximab antibody production [23]. Therefore, combined use of MTX is recommended in the marketing authorization for infliximab. In addition, two studies showed that concomitant MTX also improved the efficacy of etanercept or adalimumab [36,46].

After MTX, leflunomide is the most extensively studied conventional DMARD in combination with TNFα antagonist therapy. Data are available for infliximab [64–69] and adalimumab [70]. Studies have also evaluated cyclosporine A used with infliximab or adalimumab [43,69–72]. MTX is the only DMARD that has been studied in combination with etanercept.

3.2.4. Monitoring program to be started at initiation of TNFα antagonist therapy

A standardized monitoring program should be offered (Fig. 2, point 4). Adjusting the treatment on the basis of regularly determined DAS28 values has been shown to improve the outcome of RA [2,49]. The monitoring program was developed on the basis of the summaries of product characteristics and of recommendations issued in 2004 by another panel of experts [6,7]. Recent reports of hematological and hepatic side effects in Europe and the US prompted the recommendation that blood cell counts and transaminase levels be checked regularly. Foci of infection should be sought by history taking and physical examination. Infections should be treated promptly.

3.3. Adjusting the treatment in patients given TNFα antagonist therapy for rheumatoid arthritis

3.3.1. Treatment objective

The treatment objective was defined as achievement of the EULAR response criteria (Fig. 3, point 1). This definition is supported by the widespread use of the DAS28 in everyday practice and by findings from two controlled studies [2,49].

3.3.2. Adjustments required by inefficacy

As stated in point II.3, failure to respond to a TNFα antagonist used alone should lead to add-on therapy with a conventional DMARD (Fig. 3, point 2). MTX deserves to be given preference, as it is the most extensively studied DMARD in this situation. Add-on MTX therapy should be considered even in patients with a history of MTX discontinuation due to lack of efficacy [73]. When MTX is contraindicated, another conventional DMARD should be tried in combination with the TNFα antagonist. A DMARD previously discontinued because of side effects may deserve to be tried again, although this possibility should be discussed on a case-by-case basis.

Data from one study [42] suggest that adalimumab given at 1-week instead of 2-week intervals may produce better ACR responses. Improved responses have also been reported when infliximab was given at shorter intervals (6–7 weeks instead of 8 weeks) or in higher dosages (up to 5 mg kg^{-1} per infusion) [30,74,75]. With infliximab, the best option may be to shorten the interval when the effect wears off before the next scheduled injection and to increase the dosage when the overall effect is inadequate. However, the cost of treatment increases in proportion with the amount of medication used.

Patients who fail to respond to TNFα antagonist therapy can be switched to another TNFα antagonist. Although none of the three available compounds has been proven superior over the others, individual patients may respond better to one agent than to the others [74,76–85]. No factors predicting sensitivity to a specific TNFα antagonist have been identified to date. However, one study suggests that failure to respond to infliximab and etanercept may predict failure to respond to adalimumab [86].

3.3.3. Adjustments required by side effects

TNFα antagonists can induce class effects and/or effects specific of each individual compound (Fig. 3, point 3). When compound-specific side effects occur, the appropriateness of switching to another TNFα antagonist should be discussed on a case-by-case basis [76,79–82]. Specific management strategies for each side effect are described in the CRI fact sheets [62], which are available on the Internet at (http://www.cri-net.com/).

3.3.4. Adjustment during remissions

Nonsteroidal antiinflammatory agents and prednisone are chiefly intended to control symptoms and should be reduced or stopped during remissions. DMARDs can be decreased when a long-lasting remission occurs. However, whether the TNFα antagonist or the conventional DMARD should be reduced first is not agreed on. Although there is no standardized definition of a “long-lasting remission” most experts agree that 1 year or more is required.

4. Discussion

The recommendations presented here are intended as an aid to rheumatologists in their everyday clinical practice. They do

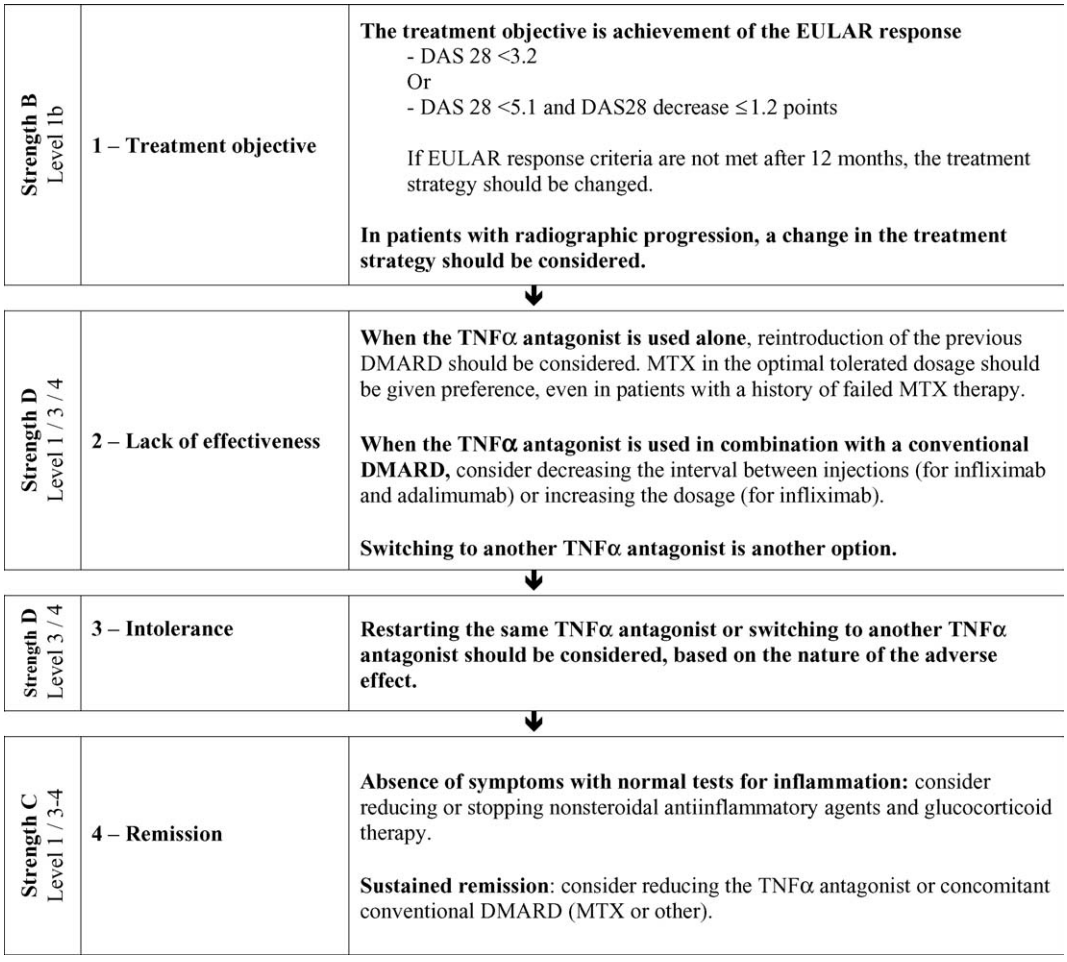


Fig. 3. Recommendations for adjusting TNFα antagonist therapy.

not constitute regulations. The simple and clear three-part algorithm format was chosen to facilitate dissemination and incorporation of the recommendations in everyday practice [87]. Recommendations for using TNFα antagonists in RA have been issued in other countries, including the UK [17], Portugal (available at http://www.spreumatologia.pt/), Italy [16], and Canada (available at http://www.cra.ucalgary.ca/), as well as internationally [15,47,88]. There are no major discordances among these sets of recommendations. Various definitions of active RA were used, such as a tender joint count greater than five with laboratory evidence of inflammation, a DAS28 greater than 5.1, or a DAS28 greater than 3.2. Radiographic progression as a criterion for TNFα antagonist use independently from the level of inflammation is included only in the Portuguese recommendations. The number of treatments to be used before considering TNFα antagonist therapy is one or two, and some recommendations require prior MTX therapy in patients without contraindications [17]. The optimal MTX dosage ranges across recommendations from 20 to 25 mg week^{-1}.

Changes in medical practices take time [18], and consequently compliance with recommendations is difficult to predict. However, with TNFα antagonists the goal is to establish practices rather than to change them. Furthermore, rheumatologists have expressed a keen interest in obtaining information about these recently introduced agents. Although regular updates will be needed, the recommendations presented here should help to optimize the management of patients with RA in a cost-effective manner.

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