Switching between anti-TNF-alpha agents does not improve functional capacity in patients with long-standing and active rheumatoid arthritis

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ABSTRACT

Objectives: To assess clinical response after switching between anti-tumor necrosis factor-alpha (anti-TNF-alpha) agents in patients with rheumatoid arthritis (RA). **Patients and methods:** This study included 99 patients diagnosed with RA (American College of Rheumatology, 1987), on anti-TNF-alpha therapy, to assess the therapeutic response after 24 weeks. Switching was performed if, after 12 to 24 weeks, a severe adverse event was reported (toxicity: T) or if no reduction greater than 0.6 in the initial Disease Activity Score 28 (DAS28) occurred (inadequate response: IR). In case of IR, the patient was considered as primary failure (PF). Secondary failure (SF) was defined as loss of response after initial improvement. Remission (DAS28 < 2.6), low disease activity (between 2.61 and 3.2), and functional improvement [increase in the initial Health Assessment Questionnaire (HAQ) > 0.2] were assessed by use of linear regression analysis. The significance level adopted was $P < 0.05$. **Results:** Switching was performed in 39 (39.4%) patients, especially due to PF (24.3%), SF (35.1%) and T (40.5%). The retention rate of the first agent was 60.1%, and the mean time for switching was 14.2 ± 10.9 months. After switching, a tendency towards a decrease in DAS28 was observed (4.7 ± 1.4; $P = 0.08$), but not in the HAQ (1.2 ± 0.77; $P = 0.11$). Around 43% of the patients achieved good/moderate EULAR response. The major determinant of switching was a higher initial DAS28, independent of age, duration of disease, and functional capacity. **Conclusion:** Switching between anti-TNF-alpha agents is a valid strategy to control disease activity, despite the low likelihood of remission and no significant improvement in functional capacity.

Keywords: rheumatoid arthritis, anti-TNF therapy, disease activity, switching, functional capacity.

INTRODUCTION

In the past decade, the treatment of rheumatoid arthritis (RA) underwent great changes with the introduction of anti-tumor necrosis factor-alpha (anti-TNF-alpha) agents, and especially with the advances in clinical and radiographic control of the disease. However, some patients either do not respond, or respond only partially, to TNF-alpha inhibitors. In addition, patients who initially responded can experience either a decrease in the efficacy of TNF-alpha inhibitors over time, or adverse events, requiring new therapeutic strategies.

In Brazil, infliximab (IFX), etanercept (ETN), and adalimumab (ADA) are currently available, being usually associated with methotrexate (MTX) or other disease-modifying antirheumatic drugs (DMARDs), except when intolerance or toxicity occurs. Although anti-TNF-alpha agents have similar clinical efficacy and costs, they differ in the following aspects: molecular structure; pharmacokinetics; mechanism of action; potential to form autoantibodies, and human anti-chimeric (HACA) or human anti-human (HAHA) antibodies; induction of apoptosis; and posology.[1–3] Thus, switching from one anti-TNF-alpha agent to another might be a treatment option

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in patients experiencing loss of efficacy or intolerance to the first treatment.[1,2]

This study aimed at assessing the clinical response, especially functional capacity, after switching from one anti-TNF-alpha agent to another in patients with active, long-standing RA, and who had failed to respond to DMARDs, including MTX.

PATIENTS AND METHODS

From January 2004 to January 2010, a retrospective analysis of the database of patients followed up at the Outpatient Clinic of Rheumatoid Arthritis and Biologics of the Discipline of Rheumatology of Escola Paulista de Medicina, Universidade Federal de São Paulo (EPM/UNIFESP), was carried out. All patients diagnosed with RA, according to the American College of Rheumatology 1987 classification criteria,[4] and on anti-TNF-alpha therapy[5] were included in the study.

Approximately 1,300 patients diagnosed with RA are annually followed up at that service, and 99 of them (7.6%) met the inclusion criteria of this study. Of those 99 patients, 39 (39%) underwent switching of the anti-TNF-alpha agent during follow-up, and were included in this analysis.

The non-inclusion criterion adopted was lack of data (initial and after six months). In addition, patients with the following characteristics were excluded: global functional status class IV;[6] inability to answer the questionnaires; other autoimmune rheumatic diseases; neoplasias; and other disabling diseases. From this cohort, only two patients were excluded, due to lack of follow-up data after switching.

The reasons for discontinuing the first anti-TNF-alpha agent were classified as follows: primary failure (PF); secondary failure (SF); adverse event (AE); and consent withdrawal (personal reasons, travel, loss to follow-up). Primary failure was defined as a DAS28 (Disease Activity Score 28) reduction lower than 0.6 after 12 weeks [no EULAR (EUropean League Against Rheumatism) response]. Secondary failure was defined as loss of efficacy (a DAS28 increase over 0.6 from the initial value) over 24 weeks in patients who had responded in the first 12 weeks, based on a DAS28 reduction greater than 0.6.[7]

Adverse event was defined as any medical occurrence not initially predicted, which appeared after switching the anti-TNF-alpha therapy. Severe AE was defined as any medical occurrence not initially predicted and that resulted in death, caused danger of death, or required or extended the ongoing hospitalization. Such events might, but not necessarily, have causal relation to the research procedures.[8]

Clinical and laboratory assessments included DAS28, erythrocyte sedimentation rate (ESR), and the Brazilian modified version of the Health Assessment Questionnaire (HAQ).[9,10] All measures were performed before treatment and three and six months after. Response to therapy was assessed according to both the DAS28 reduction and the criteria proposed by EULAR[7] (no response: a reduction lower than 0.6 between two consecutive measures; moderate: a reduction between 0.6 and 1.2; good: a reduction greater than 1.2). Clinical remission was defined as a DAS28 lower than 2.6.[10] Demographic data and disease characteristics were also included in the analysis. The synthetic DMARDs being used at the time of switching anti-TNF-alpha agents were not modified until the end of the reassessment (after 24 weeks), including stable dose and type of association.

The major risk factors associated with discontinuation were assessed by use of univariate linear regression and logistic regression. Three models were built, having the following dependent variables: HAQ (reduction of at least 0.2) in the first; moderate/good EULAR response (reduction greater than 0.6) in the second; and remission (DAS28 < 2.6) in the third. All other variables were considered as independent. For the statistical analysis, the SPSS (Statistical Package for Social Science) software, version 15.0, was used. The significance level adopted was $P < 0.05$.

RESULTS

At the end of the study, 37 patients were analyzed. Their mean age was 52 years, and the female gender predominated (89.3%). Most patients had long-standing and erosive disease, as well as high positivity for rheumatoid factor and impaired functional capacity (Steinbrocker functional class II and III)[6] (Table 1).

Table 1
Clinical and demographic characteristics of 37 patients with RA undergoing switching to a second anti-TNF-alpha agent

Age (years)	51.6 ± 11.7
Female gender (%)	33 (89.3%)
Duration of disease (months)	181.4 ± 96.4
ACR functional class	
I	3 (8.1%)
II	21 (56.8%)
III	13 (35.1%)
Positive rheumatoid factor	29 (78.4%)
Erosion on radiography (hands or feet)	31 (83.8%)

Similarly, most patients were using prednisone, at a mean daily dose of almost 10 mg. Almost 50% of the patients were using MTX in combination with TNF-alpha inhibitors, at a mean weekly dose close to 25 mg. In addition, slightly more than 80% of the patients were using leflunomide (LFN) in association with anti-TNF-alpha agents. Of those, 21.6% were on an association of LFN and MTX (Table 2).

Before using the first anti-TNF-alpha agent, almost 20% of the patients received isoniazid for treating latent tuberculous infection (LTBI), as recommended by the Brazilian Society of Rheumatology.[5] None of them had any significant AE that could determine the switching of any medication. Of the 39 patients undergoing switching between anti-TNF-alpha agents, none used isoniazid again, since no reinvestigation for LTBI was conducted prior to the introduction of the second TNF-alpha inhibitor. Thus, no association was observed between the use of isoniazid, either in the first or second time, and the AEs causing the switching between agents. However, for one patient, the switching strategy was used due to professional epidemiology (the patient is a community health agent of the Family Health Program).

The most frequently used first anti-TNF-alpha agent was IFX, followed by ETN and ADA at the same proportion (Table 2). However, most patients (69.6%) required an IFX dose increase or infusion interval reduction, to maintain the clinical benefit over time. The mean length of use of the first anti-TNF-alpha agent, prior to switching, was 14.6 ± 10.7 months. In that period, a significant decrease in DAS28 and an improvement in the functional capacity were observed (Table 3).

Table 2
Frequency of use of DMARDs and anti-TNF-alpha agents in 37 patients with RA on immunobiologic therapy

Daily dose of prednisone (mg)	9.5 ± 8.6
Weekly dose of methotrexate (mg)	23 ± 3.8
DMARDs	
Methotrexate	17 (46.8%)
Leflunomide	22 (59.5%)
Methotrexate + leflunomide	8 (21.6%)
First anti-TNF-alpha agent	
Infliximab	23 (62.2%)
Adalimumab	7 (18.9%)
Etanercept	7 (18.9%)
Second anti-TNF-alpha agent	
Infliximab	2 (5.4%)
Adalimumab	21 (56.8%)
Etanercept	14 (37.8%)

Table 3
Clinical and laboratory assessment before and after switching between anti-TNF-alpha agents

	ESR (mm/1a h)	DAS28	HAQ
First anti-TNF-alpha			
Before	35.5 ± 20.8	5.7 ± 1.2	1.2 ± 0.5
After	29.6 ± 19.5	4.6 ± 1.4	0.97 ± 0.6
P*	0.1	0.004	0.02
Second anti-TNF-alpha			
Before	36.4 ± 26.8	5.2 ± 1.3	1.4 ± 0.7
After	36.2 ± 24.2	4.7 ± 1.4	1.2 ± 0.7
P**	0.9	0.08	0.1

*Statistical difference between beginning and end of the first anti-TNF-alpha agent (Student *t* test).
**Statistical difference between beginning and end of the second anti-TNF-alpha agent (Student *t* test).

Switching between monoclonal antibodies occurred in 43.2% of the patients. In almost 40% (n = 14) of the sample, switching was from monoclonal antibodies (IFX or ADA) to soluble TNF-alpha receptor (ETN). Seven patients (18.9%) switched from the soluble receptor to monoclonal antibodies. Thus, as second anti-TNF-alpha agent, 21 patients (56.8%) used ADA, 14 (37.8%) used ETN, and only two (5.4%) used IFX (Figure 1).

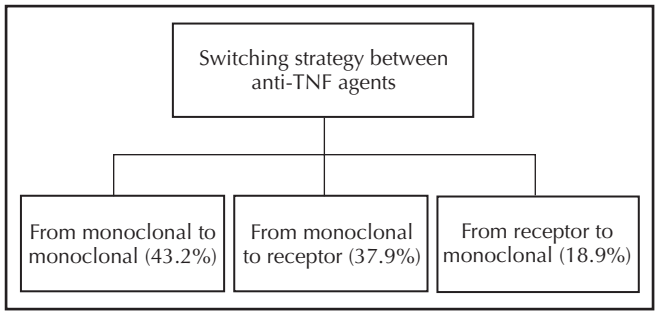

Figure 1
Switching strategy between anti-TNF-alpha agents.

Regarding the reasons for switching the first anti-TNF-alpha agent, nine patients (24.3%) had PF, 13 (35.2%) had SF, and 15 (40.5%) had AE. The major AEs motivating the switch were as follows: infusion reaction (n = 4); urticaria (n = 7); respiratory infection (n = 1); and other causes (n = 3), such as upper gastrointestinal hemorrhage and strong epidemiology for LTBI (professional contact with bacillus-carrying patients) (Figure 2). Among those switching agents due to AEs, the mean length of use of the first anti-TNF-alpha agent was 9.3 ± 6.9 months, and the mean DAS28 before and after the first anti-TNF-alpha agent were 5.9 ± 1.2 and 4.6 ± 1.1, respectively. More than half of them (54.5%) had achieved a good EULAR response, while 18.2% obtained a moderate response, and 27.3% no response. In the first

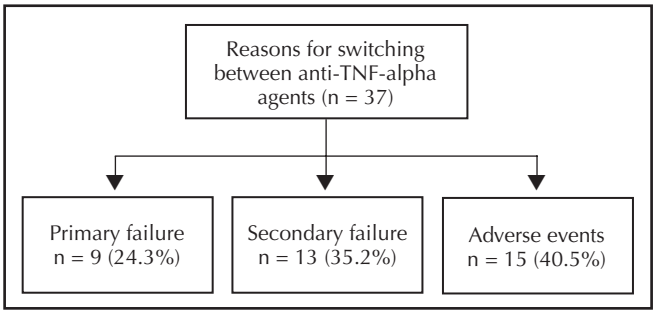

Figure 2
Reasons for switching between anti-TNF-alpha agents.

24 weeks after switching, no relevant AE was observed, even in those patients who had switched due to toxicity to the first agent.

After switching to the second anti-TNF-alpha agent, disease activity tended to improve, but at a lower magnitude than that of the first agent, according to the reduction in DAS28, but not in functional capacity (Table 3). However, using the definition of the EULAR response, 43.6% (n = 17) of the patients achieved good to moderate response after the introduction of the second anti-TNF-alpha agent, although only two (5.4%) went into clinical remission. In isolation, ESR was not a good parameter to assess the short-term laboratory response.

Only two (5.4%) patients switched the class of medication after using the second anti-TNF-alpha agent. For both, rituximab was used due to PF. None of the patients used a third anti-TNF-alpha agent.

After 24 weeks, when classifying patients according to the final DAS28 into low, and moderate/high activity, the first group had a significantly lower HAQ than that of the second group (Table 4), and also received lower doses of glucocorticoids (GC) and MTX, regardless of age, duration of disease, presence of rheumatoid factor, and erosions on radiography.

Table 4
Clinical and laboratory characteristics of the groups with low and moderate/high disease activity, according to final DAS28, after switching between anti-TNF-alpha agents

	DAS28 < 3.2	DAS28 > 3.21	P
Age (years)	52.8 ± 9.6	51.2 ± 12.3	0.81*
Initial DAS28	3.89 ± 0.57	5.48 ± 1.19	0.017*
Initial HAQ	1.04 ± 0.73	1.38 ± 0.75	0.046*
Prednisone (mg/day)	4.3 ± 9.5	9.7 ± 8.7	0.036*
Methotrexate (mg/week)	13.4 ± 5.8	21.3 ± 4.6	0.029*
Rheumatoid factor	72.4%	73.7%	0.95**
Presence of erosions on radiography (baseline)	89.2%	85.7%	0.99**

*Student *t* test. ** Fisher exact test.

Such aspects might characterize disease with better outcome and prognosis (P < 0.05).

On univariate linear analysis, age, duration of disease, and erosive disease did not significantly influence the clinical response to the second anti-TNF-alpha agent. In the final model of logistic regression for low disease activity (DAS28 between 2.61 and 3.2) and good/moderate EULAR response, none of the variables studied were significant enough to explain patients' improvement, except for a tendency towards the lowest value of the initial DAS (OR = 0.15; 95% CI: 0.02–1.26; P = 0.08). Thus, for each unit increase in the initial DAS28, there was a 85% reduction in the chance of having low disease activity after switching the anti-TNF-alpha agent, even after statistical adjustments for age, duration of disease, rheumatoid factor, initial HAQ, erosions, prednisone, MTX, anti-TNF-alpha agent, or reason for switching. The final logistic regression model for remission (DAS28 < 2.6) was not performed, because of the small number of patients.

DISCUSSION

Our results showed that the switching strategy between anti-TNF-alpha agents was performed in 39% of the patients. That frequency is slightly higher than that reported by other authors, mainly those data originating from studies of registries, in which 25%–40% of the patients discontinue treatment in the first 12 months due to loss of efficacy or AEs.[1–3,11–13] It is worth emphasizing that the long duration of disease and the high prevalence of individuals with erosive disease, although with moderate physical incapacity, characterized this cohort. Such aspects can explain the higher prevalence of that strategy.

Usually, some aspects should be considered for decision making and choosing the first or second anti-TNF-alpha agent (Chart 1). Several causes can justify switching between

Chart 1
Aspects considered for decision making and choice of anti-TNF-alpha therapy

Patient's adhesion	Patient's and physician's opinion
Patient's cognitive aspects	Convenience of application
Posology and pharmacological properties (for example, plasma and tissue half-lives)	Administration route (intravenous or subcutaneous)
Need for combined therapy with MTX or other DMARDs versus monotherapy	Potential risk of repeated or granulomatous infection (tuberculosis, leprosy, schistosomiasis)
Associated diseases, including other rheumatic diseases concomitant with RA: Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, inflammatory myopathies, vasculites	Involvement of other organs or systems: ocular, hepatic, intestinal, pulmonary, cardiac, nervous, vascular

anti-TNF-alpha agents of the same class or with a similar mechanism of action; however, usually the failure in responding (PF or SF) and the AEs are the major causes in most clinical studies published.[1,2]

Similarly to the present study, Marchesoni et al.,[13] in a large cohort of patients on anti-TNF-alpha therapy, have reported that of the 1,064 individuals assessed, 38.1% discontinued the medication. Of those, 44.4% discontinued due to inefficacy, 47.9% due to AEs, and 2.5% due to disease remission. After 36 months, ETN had the best drug survival rate (62.5%) as compared with IFX (49.1%) and ADA (53.2%). The greatest risk of discontinuing therapy due to some AE was associated with advanced age and current use of GC; while the loss of efficacy was associated with previous use of more than three DMARDs and higher ESR.[13]

In 40.5% of our patients, the reason for switching the anti-TNF-alpha agent was the presence of an AE. Usually, high retention rate of the second anti-TNF-alpha agent is observed in the first year (50%–70%), and switching from one anti-TNF-alpha agent to another can elicit an adequate clinical response, especially if caused by toxicity, as shown in a recent systematic review that assessed approximately six thousand patients.[3] A similar finding has already been reported by Hyrich et al.,[12] who, assessing patients switching the first anti-TNF-alpha agent (503 due to inefficacy and 353 due to toxicity), have shown high response and maintenance rates with the second anti-TNF-alpha agent (73%), especially when the switch was motivated by toxicity.[12] Of our 15 patients (40.5%) having AEs, five (33%) obtained a good/moderate EULAR response after the switch. Six (27.2%) of those discontinuing the use of the first anti-TNF-alpha agent due to inadequate response (59.5%) had good/moderate EULAR response. Thus, according to such data, clinical response to the second anti-TNF-alpha agent did not depend on the reason for switching (mean of 30%). In addition, toxicity of the second agent was not observed in the first 24 weeks, even in patients with severe AEs resulting from the first anti-TNF-alpha agent. It is worth emphasizing once more that anti-TNF-alpha agents are different, and switching between them is an important strategy in the clinical management of those patients.

Compared to ours, Navarro-Sarabia et al.[14] have reported a lower rate of switching to the second anti-TNF-alpha agent (19.9%), but similar frequency of good/moderate EULAR response (47%) and reasons for switching. Almost half of their patients assessed showed improvement of the HAQ (over 0.22) with the second anti-TNF-alpha agent,[14] while only 35% of our sample achieved that response. Caporali et al.,[15] assessing the data of the Italian registry of the anti-TNF-alpha agents, have also reported a lower switching rate (21.3%) than ours, especially due to PF (36.3%). Slightly more than 47% have achieved a good/moderate EULAR response after six months, and 58.6% after 12 months. Patients with high disease activity and those switching due to loss of efficacy had a greater chance to respond to the second agent.[15]

Almost 45% of our patients switched between monoclonal antibodies, a strategy less used than that including the soluble TNF-alpha receptor. Burmester et al.[16] have shown a high rate of good clinical response after 12 weeks in 358 patients who had switched from IFX to ADA, with 20% improvement in the American College of Rheumatology criteria (ACR20) in 63% of the patients, and 50/70% improvement in the ACR criteria (ACR50/70) in 35% and 12%, respectively.[16] For a longer time (six months), but with a smaller number of patients (n = 27), Wick et al.[17] have reported a similar response with the same strategy of switching between anti-TNF-alpha agents, shown as a significant reduction in DAS28 values and proportion of individuals achieving ACR20, even when compared with a third group of ADA-naïve.[17] A similar study with similar findings, during 12 months, has been published by Nikas et al.[18] and Van der Bijl et al.[19]

Switching from monoclonal antibodies to the soluble TNF-alpha receptor was performed in 37.8% of our patients. The clinical response, according to the ACR criteria, has been studied by Haraoui et al.[20] in patients with RA who had switched from IFX to ETN due to lack of efficacy or AE. ACR20/50/70 response was observed in 64%, 23%, and 5% of the patients, respectively.[20] Buch et al.[21] have switched from IFX to ETN, and, after 12 weeks, they have reported good/moderate EULAR response in 73% of the patients. It is worth noting that none of the patients who had discontinued IFX due to toxicity experienced AEs due to ETN.[21] Similar findings have also been reported by other authors.[22–24]

Almost 20% of our patients switched from the soluble TNF-alpha receptor to monoclonal antibodies. Regarding the switch from the soluble TNF-alpha receptor to monoclonal antibodies, Gomes-Reino et al.,[11] assessing data from the Spanish registry, have reported that 52 patients on ETN switched to IFX, and 14 to ADA. After 12 months, those authors have found a higher drug continuity rate with the same agent in those patients who had switched to ADA (75%) as compared with those who had switched to IFX (28%, of whom 54% discontinued due to AEs).[11] Wick et al.[17] have studied switching from ETN to ADA, with a significant reduction in the DAS28. With the same strategy and a larger sample, but with only three months of follow-up, Burmester et al.[16] have observed the ACR20/50/70 response at the proportion of 52/30/11, respectively. Scrivo et

al.[2] have also assessed the response to ADA of patients who had used ETN. After three months, 64% of the patients showed an adequate EULAR response, but almost 40% failed to respond.[2] Although with few patients, Furst et al.,[25] van Vollenhoven et al.,[26] Hansen et al.,[27] and Cohen et al.[28] have reported similar findings.

The major risk factors associated with switching between anti-TNF-alpha agents are the traditional risk factors of worse prognosis, such as poor response to DMARDs, greater number of swollen joints, longer disease duration, greater degree of disability, and persistently elevated inflammatory activity tests. Although the literature is still controversial, the presence of HACAs or HAHAs seems to be related to immuno-allergic and infusion reactions rather than to loss of efficacy.[29] In our study, only the higher disease activity, measured by DAS28, associated with worse clinical response after the switching strategy, independently of disease duration, age, physical disability, rheumatoid factor, and erosions on radiography.

More recently, Rémy et al.,[30] in a systematic review of the literature with subsequent meta-analysis of 32 relevant studies and inclusion of 4,441 patients, have shown good clinical relevance of the switching strategy between anti-TNF-alpha agents. ACR20 and EULAR responses were observed in 55.1% and 74.9% of the patients, respectively, a finding very similar to those of pivotal studies with anti-TNF-alpha-naïve individuals. Once again, the authors have confirmed previous results, in which switching due to inadequate response was associated with lower ACR20 response (54.3%) vs. switching due to AEs (62,5%). However, no significant difference was observed when that outcome was statistically assessed by use of EULAR response.[30]

Most published studies on the switching strategy to the second anti-TNF-alpha agent have assessed parameters related to improvement in clinical activity,[12,15–17,20,21,31] but not to other outcomes, such as the functional ones, remission, quality of life, and structural damage on radiography. This study, however, assesses functional capacity and remission as primary outcomes. Considering the new remission criteria recently proposed by ACR/EULAR [SDAI $\leq$ 3.3, or tender and swollen joint counts, patient's global assessment, and C-reactive protein $\leq$ 1],[32] none of our patients would meet these criteria.

Our study has some limitations, such as the retrospective design and its inherent problems, and the relatively reduced number of patients in each subgroup, after stratifying according to the reason for switching. Therefore, assessing the response effectiveness in each clinical setting was not possible. However, our study has some strong points, such as the low loss to follow-up rate and the functional capacity assessment, an outcome rarely reported in most studies. It is worth noting that, although patients had a long disease duration, they had moderate physical disability (mean HAQ < 1.5, and functional class II and III), which neither causes selection bias nor hinders the finding. Moreover, it draws attention to the greater weekly dose of MTX and greater frequency of leflunomide users, differently from that reported in the international literature.[3,11,26,33] The lack of bias of concomitant medication strengthens the role of immunobiologic agents, since the doses and type of combination of synthetic DMARCs were maintained stable for 24 weeks after switching between anti-TNF-alpha agents.

Thus, our data suggest that switching between anti-TNF-alpha agents is a valid strategy for the clinical management of patients with RA, particularly using the improvement criteria proposed by EULAR, although with low probability of remission and no significant improvement in functional capacity. However, further clinical studies, especially prospective, randomized and controlled ones, and with larger samples, are required to define the best way to manage those patients. Such studies should include the demonstration of structural benefit, gain in quality of life, and missed work days.

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