2022 French Society for Rheumatology (SFR) recommendations on the everyday management of patients with spondyloarthritis, including psoriatic arthritis

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2022 French Society for Rheumatology (SFR) recommendations on the everyday management of patients with spondyloarthritis, including psoriatic arthritis

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Abstract:

Objective: Update the French Society for Rheumatology (SFR) recommendations on the everyday management of patients with spondyloarthritis, including psoriatic arthritis.

Methods: Following standardized procedures, a systematic literature review was done by four supervised rheumatology residents based on questions defined by a task force of 16 attending rheumatologists. The findings were reviewed during three working meetings that culminated in each recommendation receiving a grade and the level of agreement among experts being determined.

Results: Five general principles and 15 recommendations were developed. They take into account pharmacological and non-pharmacological measures along with treatment methods based on the dominant phenotype present (axial, articular, enthesitis/dactylitis) and the extra-articular manifestations (psoriasis, inflammatory bowel disease, uveitis). NSAIDs are the first-line pharmacological treatment in the various presentations. Conventional synthetic disease modifying antirheumatic drugs (csDMARDs) are not indicated in the axial and isolated entheseal forms. If the response to conventional treatment is not adequate, targeted therapies (biologics, synthetics) should be considered; the indications depend on the clinical phenotype and presence of extra-articular manifestations.

Conclusion: This update incorporates recent data (published since the prior update in 2018) and the predominant clinical phenotype concept. It aims to help physicians with the everyday management of patients affected by spondyloarthritis, including psoriatic arthritis.

Keywords: spondyloarthritis, psoriatic arthritis, arthritis, enthesitis, dactylitis, treatment, recommendations

Spondyloarthritis (SpA) is a multifaceted disease [1,2]. In terms of disease classification, it encompasses various entities that were previously considered individually such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, arthritis associated with inflammatory bowel diseases (IBD) (Crohn disease, ulcerative colitis), undifferentiated SpA and juvenile forms, particularly entheseal and arthritic syndromes [3]. These various entities have common imaging and clinical manifestations, and also share pathophysiological and genetic mechanisms. SpA includes most of the presentations of PsA [4]. The latest classification criteria [5] have clearly increased awareness under the same SpA umbrella of clinical presentations or phenotypes – axial on one hand (radiographic and non-radiographic) and peripheral on the other [2] (articular, entheseal) – with the possibility of specific extra-articular manifestations, such as plaque psoriasis, uveitis or IBD, also being present.

The French Society for Rheumatology (SFR) regularly provides recommendations for the care of patients with SpA, with the last update published in 2018 [6]. New data in the treatment of axial SpA and PsA are available along with some new indications (non-radiographic axial SpA, psoriatic arthritis). Similarly, new international recommendations have provided food for thought [7-11]. While the clinical trials for PsA mainly focus on the polyarticular peripheral forms, there have been recent developments for axial manifestations of PsA [12] and peripheral forms of SpA [13]. All of this justifies that the existing recommendations be updated while grouping SpA and PsA under the same umbrella.

1. Methods

This update was carried out by following the same procedures and general principles used for the prior recommendations [6]. A project leader and task force representative of French rheumatology practice and considered as SpA disease experts was established by the SFR. Most of them were part of the previous task force [6]. The systematic literature review was performed by four university-hospital rheumatologists specifically trained in this type of analysis. The PubMed-Medline, Cochrane, Embase databases were searched in the period between May 1, 2017, and May 1, 2021 using appropriate key indexing terms. In addition, the reference lists of selected articles and proceedings of EULAR and ACR conferences were searched manually. The level of evidence of each publication was assessed. Preliminary work by the task force identified previously unrecognized issues, as well as points that required updating. The task force members then attended three in-person meetings to work on the wording of the recommendations (reformulation, reorganization, deletion or addition) based on the published data and on a discussion among the experts. Recommendations were accepted if at least 75% of the experts agreed with them, after reformulation as needed. Subsequently, the same experts

were provided with the final text of the recommendations for approval and input on their level of agreement (visual analog scale from 0–10, where 0 indicated complete disagreement and 10 complete agreement).

2. Scope

These recommendations are intended for physicians and all other healthcare professionals involved in managing patients with SpA. They apply to all adults with SpA. The pediatric and juvenile forms are the subject of their own criteria and recommendations [3,14]. This diagnosis is made by a rheumatologist based on a set of arguments from the medical history, clinical examination, laboratory tests, and imaging studies. If needed, the rheumatologist may obtain additional assistance from classification systems such as the Amor criteria or Assessment of SpondyloArthritis international Society (ASAS) criteria or CASPAR criteria [4], making sure to apply the exact definitions of each item (e.g., uveitis and/or IBD must be diagnosed by a physician) [15]. The rheumatologist's degree of confidence in the diagnosis is crucial [16]. These recommendations apply to all the clinical phenotypes, both axial (ankylosing spondylitis and non-radiographic) and peripheral (articular, entheseal, dactylitis), while including the associated extra-articular manifestations (psoriasis, uveitis, IBD). PsA is a form of SpA, thus is covered by these recommendations [2,6], which are relative to the dominant clinical phenotype (axial or peripheral) instead of the clinical disease classification.

3. Results

There is a great deal of overlap in the treatment strategy for axial SpA and PsA, thus these conditions could equally well be classified as one or the other. Consequently, a majority of the task force (75%) was in favor of setting out common recommendations that take into account the predominant clinical phenotype of the arthropathy.

Five general principles and 15 recommendations were developed.

The grade (based on the underlying level of evidence) and the level of agreement among experts (see above) are reported for each recommendation. As with the 2018 SFR recommendations, grade A recommendations were based on level 1 evidence (meta-analysis of randomized controlled trials or at least one randomized controlled trial), grade B recommendations on level 2 evidence (at least one non-randomized controlled trial or quasi-experimental study) or an extrapolation of level 1 evidence, grade

C recommendations on level 3 evidence (descriptive study) or an extrapolation of level 1 or 2 evidence, and grade D recommendations on level 4 evidence (expert opinion) or an extrapolation of level 1, 2, or 3 evidence.

3.1. General principles

3.1.1. The management and monitoring strategies should be tailored to the presentation of the disease, according to the clinical phenotype and presence of extra-articular manifestations.

This general principle was placed first to highlight the importance of recognizing the clinical presentation, which will dictate the best evaluation and treatment strategies to follow and implies that the latter will be personalized to the patient [11,17,18]. This allows us to integrate, without hierarchy or dogmatism, the various forms of SpA and PsA. This item restates the fourth general principle from the 2018 update.

3.1.2. Spondyloarthritis, including psoriatic arthritis, is a potentially severe and disabling chronic disease that has both articular and extra-articular manifestations. The rheumatologist coordinates its care, which is often multidisciplinary, in collaboration with the primary care physician and the various specialists needed.

Some forms of the disease may lead to loss or reduction of functional abilities, with potential social and professional impacts [1,4]. This principle is a reminder about potential extra-articular manifestations and places the rheumatologist in charge of managing the patient's disease. Furthermore, it highlights the importance of collaborating with other healthcare professionals (dermatologist, gastroenterologist, ophthalmologist, general practitioner).

3.1.3. The treatment goals are to improve quality of life, bring the symptoms and inflammation under control, prevent structural damage, and preserve or restore the patient's functional capabilities, autonomy, and participation in social and work-related activities.

The overall goal of treatment, whether pharmacological or non-pharmacological, is to improve the patient's quality of life (not only doing better, but doing well). Inflammation related to the disease is an important factor in the prognosis and progression of structural damage [19]. Preserving or restoring the patient's functional capacities helps the patient to continue in their occupation, among others.

3.1.4. The diagnosis must be established, and the treatment started, as early as possible.

The wording of this general principle is unchanged from 2018. An early diagnosis avoids needless, repeated diagnostic tests and doctor hopping. This also makes it possible to implement a treatment strategy after informing the patient. A window of opportunity has been discussed in SpA [20,21]. This concept is proven for peripheral SpA [22] and especially PsA [23-25]. There is also evidence in favor for axial SpA [26], with early initiation of TNF inhibitors associated with slower progression of structural damage [27]. However, the time frames are not comparable; it is months for PsA and years for axial SpA.

3.1.5. Patient information and education are an element of the disease management immediately upon diagnosis and throughout the disease course.

This is a component of the previous "Recommendation 5" which was shifted into the general principles. Information and patient education have an important role in non-pharmacological modalities [28] with evidence that it improves the care of these diseases [29]. These interventions should be carried out immediately from the start (general principle D) and must be adjusted as the disease evolves.

3.2. Recommendations

3.2.1. The goal of treatment is to achieve and maintain clinical remission, or at a minimum, a low level of disease activity in the context of shared treatment strategy.

This restates the previous "Recommendation 1", with the addition of a shared treatment strategy (which was previously included in recommendation 5). This recommendation falls within the concept of "treat to target" (T2T) which has been advocated for axial SpA and PsA [30]. Control of disease activity as evidenced or demonstrated by remission [31,32] or low disease activity is a known factor for good outcomes. This T2T notion goes hand-in-hand with that of "tight control". Arguments in favor

of positive effects of tight control on the disease are available for PsA (TICOPA) [33], and potentially also for axial SpA (TICOSPA) [34].

It is important to work with the patient to define the treatment goal from the outset. If needed, the goal can be adapted to the clinical presentation, i.e., the type and severity of the musculoskeletal and extra-articular manifestations of the disease, as well as to the patient's expectations, comorbidities, lifestyle and concerns.

3.2.2. A validated tool must be used to assess disease activity. The follow-up modalities and intervals depend on the level of disease activity and its clinical presentation.

The wording of this recommendation is unchanged. These tools can also be used to determine the response to treatment. Composite scores are generally used. For example, in axial SpA, the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and the ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score) are used in current practice. Several tools are available for PsA, with the DAPSA (Disease Activity index for PSoriatic Arthritis) being the simplest to use in clinical practice [35]. Disease remission can be defined by using thresholds – 2/10 for the BASDAI, 1.3 for the ASDAS-CRP, 4 for the DAPSA – and serve as targets for disease management. In the same vein, significant disease activity can be defined by a BASDAI above 4, ASDAS-CRP higher than 2.1, or DAPSA above 15. A response can be defined as a 50% reduction in the BASDAI (or 2 units out of 10), a decrease of more than 1.1 points on the ASDAS-CRP and 50% or greater reduction in the DAPSA. It is widely accepted, especially for DMARDs, that a relevant clinical improvement within 3 months is required to warrant continuation of the current treatment strategy and that the initial treatment goal should be achieved within 6 months. Regarding the evaluation of disease activity, the experts underlined the challenges posed by the co-existence of fibromyalgia [36-38] or residual pain/disease [39]. This combination creates diagnostic dilemmas and increases the disease activity scores, potentially resulting in over-treatment.
These indicators of disease activity are some of the data that should be collected regularly [40] to monitor the disease and during standardized periodic disease workups [10]. Regular monitoring must also assess treatment compliance and tolerance, especially for DMARDs [41].

3.2.3. Smoking cessation should be recommended routinely. Exclusion diets should not be recommended.

Smoking is a known risk factor for the occurrence, poor prognosis and worse treatment response to TNF inhibitors in axial SpA and PsA [42-45]. Thus, it is logical to request that patients stop smoking, as it will also reduce the cardiovascular, pulmonary and oncological risks related to smoking.

Exclusion diets are not indicated unless there is confirmed underlying disease (e.g., celiac disease), given the lack of data on this topic. Dietary changes aimed at weight loss are indicated in patients who are obese or overweight [46]. The SFR has recently published broad recommendations on dietary practices and chronic inflammatory rheumatic diseases that also apply to SpA [47]

3.2.4. Patients should receive screening and management for comorbidities, notably cardiovascular diseases, obesity and osteoporosis, in accordance with current recommendations.

Patients with SpA often have various comorbidities [48-50], thus screening must be a component of disease management [51]. It is particularly important to screen for cardiovascular diseases given their potential link with inflammation [52,53]. It is well known that metabolic syndrome is often present in patients with PsA [52]. Similarly, screening should be done for anxiety and depression, particularly in the context of Psoriasis [36]. Obesity and excess weight must not be ignored as they are associated with disease severity and worse response to certain classes of therapeutic molecules [54,55]. Positive effects of weight loss have been observed on the progression of PsA in obese patients [56]. Similarly, reduced bone mineral density is often present, which can lead to osteoporosis [57,58]. Management of these comorbidities, which are evaluated in the standardized periodic workup [10], is based on current recommendations in the various specific domains and must be done collaboratively with the general practitioner and other specialists (General Principle B).

3.2.5. Patients should be encouraged to be physically active. Self-directed rehabilitation exercises are recommended. Kinesitherapy should be proposed in severe forms.

Physical activity was grouped with physiotherapy and rehabilitation in this recommendation. Regular physical activity is widely recommended for all rheumatological diseases [59]. Beneficial effects on disease activity have been found for axial SpA [60,61] and PsA [62], with good tolerance for intense exercise.

3.2.6. Other than their rheumatologist, patients can get information from the multidisciplinary care team, therapeutic patient education programs, patient associations and certain digital tools.

This new recommendation highlights the relevance of therapeutic patient education and information (general principle E). It emphasizes the importance of verifying the accuracy of information sources and the benefits of therapeutic patient education programs and patient associations.

3.2.7. Analgesics can be used in the event of residual pain, in combination with other treatments.

The wording of this recommendation has not changed. The task force insisted on the importance of evaluating residual pain despite other treatments, bringing up the possibility of central sensitization phenomena secondary to chronic inflammatory diseases [63-65] and links with associated or secondary fibromyalgia [38,66,67].

3.2.8. Nonsteroidal anti-inflammatory drugs (NSAIDs) (up to the maximum dose) are indicated as the first-line treatment. When effective, NSAIDs are continued at the dosage and duration required to control the symptoms, while keeping in mind the risk/benefit ratio.

This statement reuses the terminology from the prior version. This recommendation confirms the primary role of NSAIDs in the treatment strategy for SpA, particularly axial, whether radiographic or non-radiographic [68]. The effectiveness of this therapeutic class is one of the classification criteria [5]. In the absence of contraindications, the highest recommended dose should be used initially. The chosen pharmaceutical formulation and dosing schedule should aim to minimize morning stiffness. The NSAID trial must be sufficiently long. If the effect is not satisfactory, it is important to try a different class of NSAIDs, repeating the trial several times if necessary. The 15-day course and two different NSAIDs listed in prior recommendations [6] and current international recommendations [7,8] should be considered as the bare minimum, not as a threshold for triggering the prescription of a biologic [69]. NSAIDs may have a structural effect [70]; however, the level of evidence is not sufficient to recommend continued use at full dose with the sole aim of slowing down structural damage, especially since side effects (digestive, cardiovascular, renal) are possible during prolonged use [71,72]. This justifies the

statement about the risk/benefit ratio in the recommendation. Lastly, when a biologic is added, stopping the NSAIDs is possible and desirable in patients whose disease has been stabilized by the biologic [73]. Occasional recourse to NSAIDs, in combination with the biologic therapy, is possible when the disease flares up and must be explained to the patient.

3.2.9. In most patients, systemic corticosteroid therapy is not warranted. Local corticosteroid injections can be considered, especially for treating isolated locations.

This recommendation was not changed. Recent studies of high systemic doses appear to show a small effect on axial symptoms [74] especially for PsA [75]. However, the small sample size and short follow-up means that we cannot recommend this practice. Corticosteroid injections can be proposed to patients with axial pain, especially in the sacroiliac joints, with a transient effect on symptoms [76].

3.2.10. In patients who primarily have axial manifestations and do not respond to symptomatic therapy

3.2.10.1. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs such as methotrexate, leflunomide, and sulfasalazine) are not indicated.

This recommendation is unchanged for the axial phenotype. There is no recent data suggestive of an effect on symptoms or potential beneficial structural effect on radiographs [77]. Nevertheless, when used in combination with a TNF inhibitor, methotrexate (MTX) reduces the immunogenicity of the anti-TNF agent and may increase the long-term maintenance of these drugs [78].

3.2.10.2. Targeted therapies (TNF inhibitors, IL17 inhibitors, JAK inhibitors) should be considered in patients with active axial SpA despite NSAID therapy, generally trying TNF inhibitors first.

This is a restatement of the prior Recommendation 11. For the axial phenotype, targeted therapies consist of the various TNF inhibitors (including some biosimilars), IL17 inhibitors, and JAK inhibitors. These treatments have profoundly changed how axial SpA is managed. Their introduction, if no contraindications are present, requires a long-lasting level of inflammatory activity of the axial symptoms (typically BASDAI greater than 4/10 or ASDAS-CRP above 2.1) and insufficient response to NSAID treatment (or intolerance or contraindication). Some scenarios are an additional argument to joint involvement for starting a targeted therapy (active extra-articular manifestation) (Figure 1). As stated above, the efficacy of NSAIDs must have been tested with

various different molecules over a sufficient amount of time. The indication for targeted therapy assumes a strong belief in the diagnosis on one hand, and certainty that the symptoms are related to the disease's inflammatory process (same goes for CRP).

TNF inhibitors are usually the first targeted therapy used. The task force chose not to modify this wording relative to the previous recommendations, taking into account the longer follow-up available with this class of biologics, the lower cost when biosimilars are used and the lack of head-to-head studies of TNF inhibitors versus IL17 or JAK inhibitors in axial SpA.

3.2.10.3. In patients with IBD or refractory or recurrent uveitis, the preferred treatment is a monoclonal anti-TNFα antibody, while for disabling psoriasis, the preferred treatment is an IL-17 antagonist.

Monoclonal anti-TNF antibodies are effective against certain extra-articular manifestations (IBD, uveitis) that IL-17 antagonists are not. In patients with severe associated plaque psoriasis, a monoclonal antibody against IL17A (secukinumab, ixekizumab) can be used as the first-line treatment, since these biologics provided greater skin improvements than TNF inhibitors (adalimumab) during a head-to-head comparison in PsA (SPIRIT H2H, EXCEED) [79,80].

TNF inhibitors have an equal efficacy overall on axial joint manifestations, with none being superior given the lack of comparative studies. Conversely, no effectiveness of soluble TNF receptor (etanercept) on IBD and uveitis was observed.

Two monoclonal anti-IL17 antibodies are currently indicated in axial SpA (secukinumab and ixekizumab [81,82]). They are effective against axial manifestations (and articular ones in general) and on plaque psoriasis but have no efficacy for digestive or ophthalmological conditions. Based on the results of controlled trials, these two IL17 inhibitors are equally indicated in the non-radiographic forms of axial SpA [83,84]. Secukinumab was shown to be effective on axial manifestations of PsA (Maximise study) [85]. Other IL17 inhibitors are being evaluated: bimekizumab (dual IL-17A/17F inhibitor) [86] and brodalumab (IL-17 A receptor antagonist) [87].

In controlled trials, IL-23 inhibitors had no efficacy on the axial component of SpA [88], both for ustekinumab (IL-12/23p40 monoclonal antibody) [89] and risankizumab (IL-23p19 monoclonal antibody) [90].

Among synthetic targeted therapies, apremilast was found to be ineffective against axial SpA in a controlled study [91]. Conversely, selective JAK inhibitors have achieved significant results in ankylosing spondylitis during controlled trials with upadacitinib [92] (European marketing authorization) and tofacitinib [93]. These JAK inhibitors were also effective on psoriasis (but no development or marketing authorization to come) and potentially on IBD, and also on peripheral

manifestations of PsA. Upadacitinib was found to be effective against axial manifestations of PsA (post-hoc analysis) [94]. There is currently no data on JAK inhibitors in non-radiographic axial SpA. Other selective JAK1 inhibitors (filgotinib) have been found to have good effects in ankylosing spondylitis [95].

The efficacy of these approved treatments was demonstrated on the clinical signs and symptoms, laboratory parameters (particularly CRP), and signs of inflammation on MRI (spine and sacroiliac joints). For TNF inhibitors, slowing of the structural progression is possible with long-term use (beyond 4 years) in axial SpA [96]. The therapeutic effects also extend to the patients' quality of life and various patient-reported outcome measures, along with better productivity at work, which may contribute to a positive cost/efficacy ratio.

To this day, there is no evidence that routinely adding a csDMARD to a targeted therapy prescribed for axial SpA is beneficial, especially with IL17 inhibitors, which are not very immunogenic.

Guidelines for using and monitoring targeted therapies in various situations are set forth in the CRI fact sheets available at http://www.cri-net.com

These treatments require that information be provided to the patient and the other healthcare professionals, which falls within therapeutic patient education, and that regular surveillance be done to detect potential secondary or paradoxical effects.

The therapeutic effects should be evaluated using validated tools after 3 months, based on the threshold values listed in recommendation 2. If no significant improvement is apparent after 3 months, changing the treatment should be considered. If the 6-month goal of clinical remission or low disease activity is not achieved, the treatment must be changed.

3.2.10.4. If there is no evidence of structural damage in the sacroiliac joints with no evidence of inflammation in laboratory tests or on MRI, targeted therapies are not indicated, except in highly selected patients.

This is a restatement of the second part of the previous "recommendation 11" [6]. It is based on the same argument of lack of significant difference between TNF inhibitors (adalimumab, golimumab) and placebo during prospective controlled trials in non-radiographic axial SpA with normal CRP and no findings of inflammation on MRI [6]. This was confirmed in a recent study with etanercept in the same disease profile [97]. There is currently no data for IL17 antagonists or JAK inhibitors, thus no indication for starting these treatments in this situation. However, the task force believes that some very unique cases will warrant a collegial discussion and shared decision-making.

3.2.11. In cases of peripheral arthritis unresponsive to symptomatic therapy

3.2.11.1. Treatment with csDMARDs should be considered if NSAIDs have failed, along with local interventions. In cases of psoriasis, methotrexate is the preferred treatment.

In this scenario, recourse to MTX is accepted by experts, despite the low level of evidence. There is no evidence of MTX having a structural effect [98]. There is a known effect on plaque psoriasis. The studies of sulfasalazine are older, the clinical efficacy is moderate and there is no marketing authorization for this indication. Leflunomide has clinical efficacy but no structural effects, with only a modest effect in psoriasis.

3.2.11.2. In patients who do not respond to conventional treatments, or have structural damage, active IBD or refractory/recurrent uveitis, a targeted therapy must be considered (Figure 1)

The severity of the articular and/or extra-articular manifestations justifies this recourse. The severity of PsA is defined by multiple joint involvement, elevated CRP levels, radiographic changes, presence of nail psoriasis or associated dactylitis [8].

Various studies have shown that targeted therapies are effective in this scenario (anti-TNF, anti-IL-17, anti-IL-23, JAK inhibitors) [9, 99-109].

Note that abatacept was granted marketing authorization in Europe based on a controlled study in peripheral PsA but is not reimbursed in France; its joint efficacy was moderate (ACR 20) and the skin effects were modest [108].

3.2.11.3. When turning to a targeted therapy, the preferred first line treatments are TNF inhibitors or IL17 antagonists.

Head-to-head studies of IL17 antagonists versus TNF inhibitors in PsA showed that both had similar efficacy on arthritis, while IL17 antagonists were better on skin manifestations (see 10C). Anti-IL23 antibodies and JAK inhibitors can be proposed as second-line treatments. These targeted therapies can slow the progression of structural damage in PsA, although the extent varies by molecule [103].

3.2.11.4. In patients with IBD or refractory/recurrent uveitis, the preferred treatment is a monoclonal anti-TNF antibody.

This suggestion is based on the fact that anti-TNF agents are the class of molecules that have the largest body of evidence with these two extra-articular manifestations. See 10C

3.2.11.5. In patients with disabling psoriasis, the preferred treatments are selective IL-17, IL12/23 or IL23 antagonists.

These targeted therapies have better efficacy for cutaneous manifestations than TNF inhibitors in head-to-head studies (see 10.C)[79,80]. Severe PsA can be defined by its expanse, location (visible, genital, ungual, palmar/plantar) or its psychological, social or functional repercussions.

3.2.11.6. In cases of associated axial manifestations, the preferred treatments are anti-TNF, anti-IL17 or JAK inhibitors.

These targeted therapies have demonstrated efficacy against peripheral and axial manifestations. IL23 inhibitors were not effective on axial manifestations in controlled trials (see 10.C)[104,110]. If an oral medication is preferred, the first choice is JAK inhibitors.

3.2.11.7. Apremilast can be considered for patients with psoriatic arthritis if the disease is not classified as severe (no structural damage) and is unresponsive to conventional treatments (figure 2)

This phosphodiesterase-4 inhibitor has marketing approval in Europe in moderate PsA that has failed MTX treatment. It is reimbursed in this indication. There is no data on effectiveness against structural progression [111].

3.2.11.8. Methotrexate should not be used routinely with targeted therapies.

Various controlled studies of targeted therapies have not found an increase in the percentage of responders when MTX was added to the treatment regimen compared to monotherapy [112,113]. However, cohort and registry-based studies have found better treatment retention and higher remission rate with anti-TNF antibodies[114] when they are combined with MTX. Consequently, MTX can be continued even when an anti-TNF antibody treatment is started (expert opinion).

3.2.12. In patients with enthesitis and/or dactylitis that does not respond to symptomatic treatment

3.2.12.1. Conventional synthetic DMARDs are not indicated.

In fact, there is no evidence that this therapeutic drug class is effective against isolated enthesitis or dactylitis.

3.2.12.2. In patients with enthesitis definitely attributed to SpA, or dactylitis that does not respond to symptomatic treatment, a targeted therapy (anti-TNF, anti-IL-17, anti-IL-12/23, anti-IL-23, JAK inhibitor) should be considered.

Post-hoc analyses or evaluations of secondary endpoints from controlled studies [115,116], along with studies specifically focused on enthesitis [117] or dactylitis [118] have found that targeted therapies are effective against these clinical manifestations.

3.2.13. In all clinical phenotypes, if the first targeted therapy is not effective, all the reasons other than the SpA itself must be ruled out (compliance, mechanical pathology, fibromyalgia) before a second targeted therapy can be considered.

If the response to the first targeted therapy is insufficient, the type and reason(s) for the failure must be analyzed (primary lack of effectiveness, loss of efficacy, intolerance, poor compliance, etc.). The element used to define the insufficient response (residual pain, polyalgia syndrome, etc.) (see Recommendation 7) and potential factors that could interfere with how the response was evaluated should be explored. If the disease's inflammatory activity persists (treatment goal not met), a shift to another targeted therapy can be considered. Registry and cohort studies, along with Phase III clinical trials, have shown that a second biologic (TNF inhibitors or IL17 inhibitor after a first or second TNF inhibitor) can help to achieve a positive outcome, although the percentage of responders will be slightly lower than with the first line therapy. These findings also revealed a better overall response when the first-line therapy had failed because of side effects instead of failing due to lack of efficacy [119,120]. In case of primary lack of effectiveness of the first TNF inhibitor, it seems logical to change targets and shift to an IL17 inhibitor.

In case of partial response, adjusting the dosage (increase dose or reduce dosing interval) of the biologic could be considered in certain situations. The dosage can be doubled for golimumab if the patient weighs more than 100 kg (220 lbs.) and for secukinumab if the response is not sufficient for ankylosing spondylitis or if psoriasis is also present.

In case of secondary loss of efficacy to the first TNF inhibitor, an alternative TNF inhibitor or an IL17 inhibitor can be proposed [119,120]. Registry data point to no clear difference between these two options [121,122]. A prospective randomized multicenter trial is underway in France.

3.2.14. In all clinical phenotypes, in patients who have achieved disease remission or low level of activity for at least 6 months with biologic therapy, gradually increasing the dosing interval or decreasing the dose can be considered.

This recommendation is unchanged relative to the 2018 version. Discontinuing the treatment is virtually always followed by a relapse in the following months. Recent data have added to the discussion about axial SpA. For TNF inhibitors, an open, non-randomized study showed that, in a population of patients with low disease activity, the outcome was the same over 1 year between continuing with the same regimen and increasing the dosing interval [123]. In the C-Optimise follow-up study of patients in remission, their condition was stable for 1 year when the certolizumab dose was reduced by 50% [124]. However, the experts remind us that a higher risk of disease flares/relapses has been observed when the dose of TNF inhibitors is reduced [125]. The SPACING study is a randomized prospective trial evaluating, in patients who have low disease activity for at least 6 months, standard dosing or increased dosing intervals for TNF inhibitors, with follow-up every 3 months and adjustment of the interval (longer or shorter) based on the disease activity, over 12 months [126]. Statistical non-inferiority was demonstrated: among the 373 patients who had the full follow-up (94%), 88% (162/184) had low disease activity in the "spacing" group versus 91% (173/189) in the "unchanged" group at 12 months.

With IL17 inhibitors, the randomized, controlled COAST-Y study evaluated stopping ixekizumab completely versus continuing the standard regimen for patients with axial SpA in remission. Continuing the treatment was associated with a lower risk and longer time to appearance of the first flare relative to the withdrawal group; however there was no difference between the two groups during the first 40 weeks of follow-up [127]. In the peripheral forms of PsA, similar observations were reported with ixekizumab [128].

3.2.15. Surgery can be considered to treat advanced joint destruction, spinal fusion with major deformity or vertebral fractures.

This recommendation is largely unchanged. Recourse to surgery can be discussed in certain situations, although these are becoming increasingly rare [129-132].

4. Discussion

This work resulted in a revision of the 2018 SFR recommendations about the management of patients with SpA, including PsA and is summarized in Table I. In accordance with the objective, these capture most scenarios by taking into account the clinical phenotype and whether any extra-articular manifestations are present, along with their level of activity or severity. These recommendations are

intended to assist the health care professional who is faced with a complex disease and an ever-growing number of treatment options; they cannot be used for administrative or medicolegal purposes. Questions came up while we were formulating these recommendations that do not yet have a definite answer. These were included in the research agenda (Box 1). The next steps are the dissemination and implementation of this update. Further updates to these recommendations are already planned by the SFR, although the time frame will depend how quickly our knowledge and concepts evolve and the results of on-going studies.

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Table I: Summary with strength of evidence grade and level of agreement among experts

General principles and recommendations	Grade	Level of agreement	
General principles			
A. The management and monitoring strategies should be tailored to the presentation of the disease, according to the clinical phenotype and presence of extra-articular manifestations.	B	9.9	
B. SpA, including PsA, is a potentially severe and disabling chronic disease that has both articular and extra-articular manifestations. The rheumatologist coordinates its care, which is often multidisciplinary, in collaboration with the primary care physician and the various specialists needed.	C	9.7	
C. The treatment goals are to improve quality of life, bring the symptoms and inflammation under control, prevent structural damage, and preserve or restore the patient's functional capabilities, autonomy, and participation in social and work-related activities.	B	9.8	
D. The diagnosis must be established, and the treatment started, as early as possible.	B	9.8	
E. Patient information and education are an element of the disease management immediately upon diagnosis and throughout the disease course.	B	9.8	
Recommendations			
1. The goal of treatment is to achieve and maintain clinical remission, or at a minimum, a low level of disease activity in the context of shared treatment strategy.	C	9.7	
2. A validated tool must be used to assess disease activity. The follow-up modalities and intervals depend on the level of disease activity and its clinical presentation.	C	9.0	
3. Smoking cessation should be recommended routinely. Exclusion diets should not be recommended.	B	9.5	
4. Patients should receive screening and management for comorbidities, notably cardiovascular diseases, obesity and osteoporosis, in accordance with current recommendations.	C	9.1	
5. Patients should be encouraged to be physically active. Self-directed rehabilitation exercises are recommended. Kinesiotherapy should be proposed in severe forms.	B	9.5	
6. Other than their rheumatologist, patients can get information from the multidisciplinary care team, therapeutic patient education programs, patient associations and certain digital tools.	C	9.3	
7. Analgesics can be used in the event of residual pain, in combination with other treatments.	B	9.5	
8. Nonsteroidal anti-inflammatory drugs (NSAIDs) (up to the maximum dose) are indicated as the first-line treatment. When effective, NSAIDs are continued in the dosage and duration required to control the symptoms, while keeping in mind the risk/benefit ratio.	A	9.7	
9. In most patients, systemic corticosteroid therapy is not warranted. Local corticosteroid injections can be considered, especially for treating isolated locations	C	9.1	
10. In patients who predominantly have axial manifestations and did not respond to symptomatic therapy			
A. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs such as methotrexate, leflunomide, and sulfasalazine) are not indicated.	A	9.7	
B. Targeted therapies (anti-TNF, anti-IL17, JAK inhibitors) should be considered in patients with active axial SpA despite NSAID therapy, generally trying TNF inhibitors first.	A	9.4	

C. In patients with IBD or refractory or recurrent uveitis, the preferred treatment is a monoclonal anti-TNFα antibody, while for disabling psoriasis, the preferred treatment is an IL-17 antagonist. D. If there is no evidence of structural damage in the sacroiliac joints with no evidence of inflammation in laboratory tests or on MRI, targeted therapies are not indicated, except in highly selected patients.	B A	9.4 8.8	
11. In cases of peripheral arthritis unresponsive to symptomatic therapy			
A. Treatment with csDMARDs should be considered if NSAIDs have failed, along with local interventions. In cases of psoriasis, methotrexate is the preferred treatment.	B	9.0	
B. In patients who do not respond to conventional treatments, or have structural damage, active IBD or refractory/recurrent uveitis, a targeted therapy must be considered.	A	9.7	
C. When turning to a targeted therapy, the preferred first line treatments are TNF inhibitors or IL17 antagonists.	A	9.0	
D. In patients with IBD or refractory/recurrent uveitis, the preferred treatment is a monoclonal anti-TNF antibody.	A	9.3	
E. In patients with disabling psoriasis, the preferred treatments are selective IL-17, IL12/23 or IL23 antagonists.	B	9.2	
F. In cases of associated axial manifestations, the preferred treatments are anti-TNF, anti-IL17 or JAK inhibitors.	B	9.2	
G. Apremilast can be considered for patients with psoriatic arthritis if the disease is not classified as severe (no structural damage) and is unresponsive to conventional treatments.	B	8.8	
H. Methotrexate should not be used routinely with targeted therapies.	B	8.7	
12. In patients with enthesitis and/or dactylitis that does not respond to symptomatic treatment			
A. Conventional synthetic DMARDs are not indicated.	B	9.2	
B. In patients with enthesitis definitely attributed to SpA, or dactylitis that does not respond to symptomatic treatment, a targeted therapy (anti-TNF, anti-IL-17, anti-IL-12/23, anti-IL-23, JAK inhibitor) should be considered.	A	9.5	
13. In all clinical phenotypes, if the first targeted therapy is not effective, all reasons other than the SpA itself must be ruled out (compliance, mechanical pathology, fibromyalgia, etc.) before a second targeted therapy can be considered.	A	9.7	
14. In all clinical phenotypes, in patients who have achieved disease remission or low level of activity for at least 6 months with biologic therapy, gradually increasing the dosing interval or decreasing the dose can be considered.	B	9.6	
15. Surgery can be considered to treat advanced joint destruction, spinal fusion with major deformity or vertebral fractures.	C	9.0	

Box 1. Research agenda

- Impact of self-assessment / self-management in disease care
- Relevance of imaging in the management of mono-enthesitis / dactylitis
- Role of MTX in peripheral forms as a function of the initial targeted therapy
- Parameters of the physical therapy intervention as a function of clinical phenotype and disease severity
- Treatment strategy for second-line targeted therapy
- Evaluate anti-TNF after anti-IL-17 in axial SpA
- Evaluate efficacy of anti-IL17 and JAK inhibitors in axial SpA with no objective signs of inflammation
- Head-to-head studies of anti-TNF/ anti-IL17 in axial SpA
- Evaluate JAK inhibitors in non-radiographic axial SpA
- Results of other IL17 inhibitors: bimekizumab, brodalumab
- Results of other IL23 inhibitors: risankizumab, tildrakizumab
- Develop new biomarkers of disease activity and treatment response
- Role of biomonitoring in the treatment strategy of biological DMARDs
- Predictors of a response with anti-IL17, anti-IL23 and JAK inhibitors
- Optimal use of NSAIDs
- Relevance of anti-IL17/IL23 loading dose
- Effect of biologics and targeted therapies on structural progression in axial forms
- Health economics of using biologic drugs and targeted therapies

Figure 1: Indication for a targeted therapy

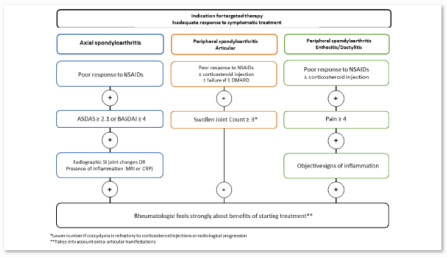

Figure 2: Overall treatment strategy for spondyloarthritis, including psoriatic arthritis. The numbers in parentheses refer to specific recommendations

At each step:

- If goal achieved or response occurs (50% reduction in disease activity): continue as is
- If goal not achieved or response insufficient: go to next step (13)
- If sustained remission (at least 6 months): option to increase dosing interval (14)