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2024 update of the recommendations of the French Society of Rheumatology for the diagnosis and management of patients with rheumatoid arthritis

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DMARD; Interstitial lung disease; JAK inhibitors; Management; People at risk of rheumatoid arthritis; Recommendations for clinical practice; Rheumatoid arthritis; Targeted therapies; Therapeutics; biologics.

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Abstract

The French Society of Rheumatology recommendations for managing rheumatoid arthritis (RA) has been updated by a working group of 21 rheumatology experts, 4 young rheumatologists and 2 patient association representatives on the basis of the 2023 version of the European Alliance of Associations for Rheumatology (EULAR) recommendations and systematic literature reviews. Two additional topics were addressed: people at risk of RA development and RA-related interstitial lung disease (RA-ILD). Four general principles and 19 recommendations were issued. The general principles emphasize the importance of a shared decision between the rheumatologist and patient and the need for comprehensive management, both drug and non-drug, for people with RA or at risk of RA development. In terms of diagnosis, the recommendations stress the importance of clinical arthritis and in its absence, the risk factors for progression to RA. In terms of treatment, the recommendations incorporate recent data on the cardiovascular and neoplastic risk profile of Janus kinase inhibitors. With regard to RA-ILD, the recommendations highlight the importance of clinical screening and the need for high-resolution CT scan in the presence of pulmonary symptoms. RA-ILD management requires collaboration between rheumatologists and pulmonologists. The treatment strategy is based on controlling disease activity with methotrexate or targeted therapies (mainly abatacept or rituximab). The prescription for anti-fibrotic treatment should be discussed with a pulmonologist with expertise in RA-ILD.

1. Introduction

The 2024 update of the recommendations of the French Society of Rheumatology (Société française de rhumatologie [SFR]) is the third edition of the French recommendations for the diagnosis and management of rheumatoid arthritis (RA), following those of 2014[1] and 2018 [2]. Regular recommendation updates are required in light of the large volume of scientific publications on both the diagnosis and therapeutic management of the disease. An update every 3 to 5 years is the usual frequency recommended in this field [3–5]. The 2024 update is 6 years after the last published recommendations because of the COVID-19 epidemic and the publication of alerts by the US Federal Drug Agency (FDA) and the European Medicines Agency (EMA) on the safety of some targeted disease-modifying anti-rheumatic drugs (tDMARDs). The SFR decided to postpone the updating process in order to incorporate the conclusions of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) [6].

As in 2018, the 2024 update used as starting points the European Alliance of Associations for Rheumatology (EULAR) recommendations (i.e., the 2016 and 2023 recommendations on RA diagnosis and management) and the 2016 recommendations on early arthritis [7–9]. In other words, the systematic literature reviews (SLRs) performed under the aegis of EULAR were repeated [10–12] and completed for the additional period from January 2022 to May 2023.

As with previous recommendations, the 2024 French recommendations aim to cover all areas of RA management: diagnosis, treatment, follow-up, remission and comorbidities management. In the engagement letter issued by the SFR, 2 new themes were added for the 2024 update:

- management of pre-RA (i.e., people at risk of RA [PARRA] because of a family history of RA or the presence of RA-related autoantibodies);
- RA-associated interstitial lung disease (RA-ILD), both in terms of screening and therapeutic management.

The SFR recommendations are primarily intended for rheumatologists but may also be of importance to any physician, healthcare professional or medical student caring for people with RA; patients and their representative associations; and healthcare authorities.

The final aim of this work was to update and complete the SFR recommendations for the diagnosis and management of RA and its complications, with the ultimate goal of improving the quality of care for people living with RA.

2. Methods

In 2022, the SFR commissioned an academic rheumatologist (BF) to coordinate the updating of the 2018 recommendations on the management of RA, incorporating 2 topics not addressed in the latest recommendations. First, the management of “pre-RA”, currently called PARRA because RA will develop in only a few of these people, was added to the scope of this update. This topic was the subject of several recommendations or consensus statements by EULAR to

address a few important points: the terminology to be used, quantification of the risk of the disease developing, and clinical research strategy for such people [13–15]. Second, the management of ILD associated with RA (RA-ILD) was included. Rheumatologists often face difficulties caring for such patients, and although international recommendations have been discussed, no consensus has been reached or published.

A working group was set up and its composition validated by the SFR board. It included 2 associate coordinators. One (CD), who coordinated the 2018 update of the SFR recommendations, has internationally recognized expertise in the field of PARRA. The other (PD) has internationally recognized expertise in RA-ILD. Four young rheumatologists were identified for the SLRs: 2 for the therapeutic aspects of RA management (JK, JD), 1 for the PARRA topic (CR) and 1 for the RA-ILD topic (PAJ). The group also included 15 university hospital rheumatologists (JA, AB, GCA, AC, CGV, VG, JEG, BLG, HM, CR, JHS, AS, RS, AT, OV), 2 non-university hospital rheumatologists (OB, ED), 1 private practice rheumatologist (ES) and 2 people living with RA and members of patient associations (PE, DV). All group members were French-speaking and lived in France or Monaco.

2.1. General procedure for drafting updated recommendations

To fulfill the mission, 4 live or virtual meetings were needed. An initial virtual scoping meeting was held in January 2023 to:

- present the French Haute Autorité de Santé methodology [16] chosen to be used in the update;
- recall the previous recommendations on which the update were based [2,9];
- define the framework for the SLRs by defining the questions and the relevant research equations needed.

During this meeting, the working group agreed to focus the literature search on:

- quantifying the risk of RA;
- the therapeutic management of PARRA with musculoskeletal symptoms (15 of 23 votes in favor, 65.2%), thus excluding the question of risk assessment in asymptomatic first-degree relatives;
- screening for RA-ILD;
- RA-ILD therapeutic management (21 of 23 votes in favor, 91.3%), without addressing the full range of RA-related pulmonary disorders.

A face-to-face meeting to develop the updated version of the recommendations took place in September 2023, supplemented by another virtual meeting to agree on the recommendations for all areas covered by the update work. A fourth and final virtual meeting was held in October 2023 for a few residual editorial changes.

2.2. Systematic review of the scientific literature

Three SLRs were performed to answer the following therapeutic questions:

- efficacy of conventional and targeted DMARDs;
- tolerability of DMARDs;
- efficacy and tolerability of glucocorticoids (GCs).

To this end, the corresponding EULAR systematic reviews[10,12,17] were updated using the same search equations, article inclusion and exclusion criteria, and study bias assessment tools[18,19]. The databases used were PubMed MEDLINE, EMBASE and Cochrane, over a period extending from January 1, 2022 to May 31,2023. Two readers (JK, BF) selected titles and abstracts by using Rayyan software (www.rayyan.ai), with consultation between the 2 readers in the event of disagreement. Two readers (JK, JD) read full texts and extracted article data.

Two SLRs were conducted to answer the questions related to PARRA. The first was predictors of the development of RA in current practice enabling quantification of the risk of RA in symptomatic individuals. Again, the search consisted of an update of the EULARSLR performed up to 2019 [14]. The second was the efficacy and tolerability of therapeutic interventions to prevent the onset of RA in PARRA. Efficacy data on symptom modification and/or impact as well as treatment tolerability were also collected when available. For these 2 reviews, 2 readers (CD, CR) searched PubMed MED-LINE as well as abstracts of the SFR, EULAR and American College of Rheumatology (ACR) congresses from January 1, 2019 to June 2023.

Finally, the same databases were used for the following SLRs relating to RA-ILD from July 2021, the date of the last literature review [20], to July 2023

- factors associated with a high risk of development of RA-ILD;
- factors associated with the severity of RA-ILD;•diagnostic performance of alternatives to thoracic CT for the diagnosis of RA-ILD;
- efficacy and tolerability of RA treatments for RA-ILD.

The search equations used for the SLRs, the flow diagrams used to select the references and the tables summarizing the SLR results are available in supplementary documents 1, 2, and 3.

2.3. Building consensus and formulating updated recommendations

The working group updated the French recommendations in September 2023, then finalized them after several rounds of e-mails and virtual meetings. This work specifically focused on recommendations for which new data were available as well as on the 2 new topics not previously addressed (PARRA and RA-ILD). During the development phase, the working group experts voted on the updated recommendations: if votes in favor represented more than

75% of the votes, the recommendation was accepted; if this percentage was not reached, discussions on modifications were extended until the required threshold was reached.

The working group continued to use the level of evidence (LoE) approach of the Oxford Centre for Evidence-Based Medicine/AGREEII [21], corresponding to EULAR's standard operating procedures[5]. After the meeting, the results were summarized and the formulation was voted on in the form of a table with the respective LoE and strength of recommendation. This table was sent to working group members to anonymously vote on the level of agreement(LoA) with each overarching principle and recommendation on a scale from 0 to 10 (0, no agreement, and 10, total agreement).

The statements were then reviewed by a reading group consisting of physicians, health professionals or patients external to the working group. The group consisted of rheumatologists in hospitals (n = 22) or private practice (n = 24), nurses or other health professionals (n = 10) and patients (n = 10). The members of this reading group voted on each recommendation using a numerical scale from 0 to 10 (0, incomprehensible or unsuitable wording of the recommendation, and 10, completely comprehensible and suitable wording). Comments were taken into account in the wording of certain recommendations and in the text.

Finally, all members of the working group provided a comprehensive list of their conflicts of interest on a public declaration-of-interest form.

3. Results

Overarching principle A

The management of RA or clinical suspicion of RA requires collaboration between the patient and the rheumatologist, within the framework of shared medical decision-making based on patient information and education.

This principle has been the first overarching principle of the recommendations since 2014 and has been maintained in the same place given the importance of the “shared medical decision” paradigm in establishing the therapeutic alliance between the patient or their caregivers on the one hand and the medical team on the other, an indispensable element of optimal care [1, 2, 22, 23]. The key elements in achieving this alliance are a consultation to explain the diagnosis; to inform and educate the patient about the disease, its consequences and challenges as well as therapeutic options; and to define the therapeutic project [24]. This process should be repeated when a new therapy is introduced [23, 24]. Information and education initiatives can be facilitated by introducing patients to RA patient associations and their representatives [23].

In this 2024 version, the experts integrated into this overarching principle the PARRA group, who are specifically symptomatic people, for whom information on symptoms requiring prompt consultation and education about modifiable risk factors are essential elements of their care [25].

Overarching principle B

The rheumatologist is the specialist who should manage RA or clinical suspicion of RA. The general practitioner plays an important role in detecting the disease and monitoring the patient in coordination with the rheumatologist.

This principle remained quasi-unchanged since the 2018 version of the SFR recommendations. It is also aligned with the EULAR recommendations for RA management [9]. Its aim is to clearly identify the 2 central medical players in management, with their respective responsibilities. The specialist rheumatologist has a major role in the rapid confirmation of the diagnosis and the choice and implementation of treatment within an optimal time-frame; several scientific studies have demonstrated the validity and robustness of this principle [26, 27]. General practitioners (GPs) have a key role in detecting the first clinical signs suggesting inflammatory rheumatism; they can also play a part in the renewal of certain treatments, particularly symptomatic ones, and the management of comorbidities [2, 8, 27].

Collaboration between rheumatologists and GPs is intended to create a genuine care pathway for RA patients, enabling personalized, coordinated patient support. Such care can obviously be a challenge in regions with a low density of rheumatologists and/or GPs. Here again, the experts have included PARRA, for whom risk assessment and management requires the expertise of the rheumatologist.

Overarching principle C

Any person with RA or clinical suspicion of RA should benefit from comprehensive, patient-centered drug and non-drug management.

This principle is taken from the 2018 SFR recommendations [2] but has been made more impactful by focusing on 2 concepts: the need for comprehensive management and the identification of both drugs and non-drug treatments (physical treatments, rehabilitation, occupational therapy, foot medicine/podology, technical aids, orthoses, surgery, psychologist management, etc.) in the therapeutic arsenal [8,25]. The elements present in the 2018 recommendations and removed from this general principle are now addressed in Recommendation 14.

Overarching principle D

To optimize the overall management of RA, the rheumatologist must take into account the costs associated with RA and its consequences.

This principle was reworded, but its meaning has been retained. Because the healthcare budget is a single envelope, all the financial consequences of an illness (consultations, hospitalizations, additional investigations, treatments, sick leave) are on the same level [28,29]. The functioning of the healthcare system can only be improved by rational and optimal patient care. Treatment decisions must be based on the efficacy and tolerability of the therapies prescribed, their cost, and the costs associated with the disease that can be avoided by putting it into remission [28–33]. With this in mind, care should favor the widespread use of biosimilars, whose equivalence has been demonstrated in terms of both efficacy and safety [33, 34]. Similarly, once remission has been achieved, gradual therapeutic tapering strategies can be integrated into this cost-cutting dynamic [35, 36]. Of note, this general principle was also reaffirmed in the 2023 EULAR recommendations [9].

Recommendation 1

The diagnosis of RA requires the presence of at least one clinical arthritis and should be confirmed as soon as possible by the rheumatologist.

In case of suspected RA without any clinical arthritis, the risk of progression to RA should be assessed on the basis of clinical, immunological and imaging criteria.

(Level of evidence IIb, grade B).

As compared with the previous SFR recommendations, the working group wanted to integrate the notion of individuals at risk of RA. To clarify the situations between individuals meeting the 2010ACR/EULAR classification criteria for RA, those at risk of persistent arthritis and those without any arthritis, we have added a diagnostic algorithm (Fig. 1), a minimal set of workups to be performed when RA is suspected (Table 1) and a list of items for assessing the risk of RA in a person with clinically suspect arthralgia (Table 2).

Risk factors for persistent arthritis were taken from the EULAR recommendations on recent arthritis updated in 2016 [8]. We wanted to emphasize the importance of clinical arthritis, which cannot be replaced by sub-clinical arthritis (detected on ultra-sonography or MRI) in the decision tree. Indeed, Dutch cohorts of individuals presenting arthralgia without clinical arthritis showed that this leads to over-diagnosis of RA and therefore possible over-treatment of patients in whom RA will not develop [37]. Among anti-citrullinated protein antibody (ACPA)-positive individuals with subclinical synovitis, in 44% to 68% of those receiving no treatment, arthritis did not develop by the 3-year follow-up.

Most of the working group agreed that differential diagnoses should be eliminated primarily during the rheumatologist assessment because some diagnoses require clinical expertise. However, this process does not exclude the role of the GP. The systematic performance of thoracic imaging was discussed (Table 1). The working group wanted to include this imaging in the minimal work-up, to eliminate certain differential diagnoses such as sarcoidosis, lymphoma or tuberculosis. Given the low sensitivity of thoracic radiography for the above diagnoses, the working group wanted to mention low-dose thoracic CT, which could replace thoracic radiography depending on accessibility and context.

Table 2 shows the 4 main areas of factors to be considered when assessing the risk of RA [38–42]. The first area concerns modifiable environmental risk factors, which should be investigated and corrected (see recommendation 2). Among occupational exposures, exposure to mineral silica is the best-documented (building trades, stone-cutting, ceramics, dentistry, etc.); it is associated with a doubling of the risk of immuno-positive RA [38]. Other occupational airborne exposures (insecticides, fungicides, welding fumes, toluene, inorganic dusts, etc.) seem to be associated with increased risk [39, 40], with a dose effect and a synergistic effect with smoking and genetic predisposition. The working group wanted to highlight certain risk factors, in particular smoking and occupational exposure, to show that not all these risk factors have the same impact. The group discussed whether periodontitis should also be highlighted, but current data are not robust. Indeed, although most studies found increased risk of RA associated with periodontitis, both genetic and environmental risk factors are common to these 2 pathologies. As a result, uncertainty persists as to a potential causal link between periodontal disease and the development of RA [41].

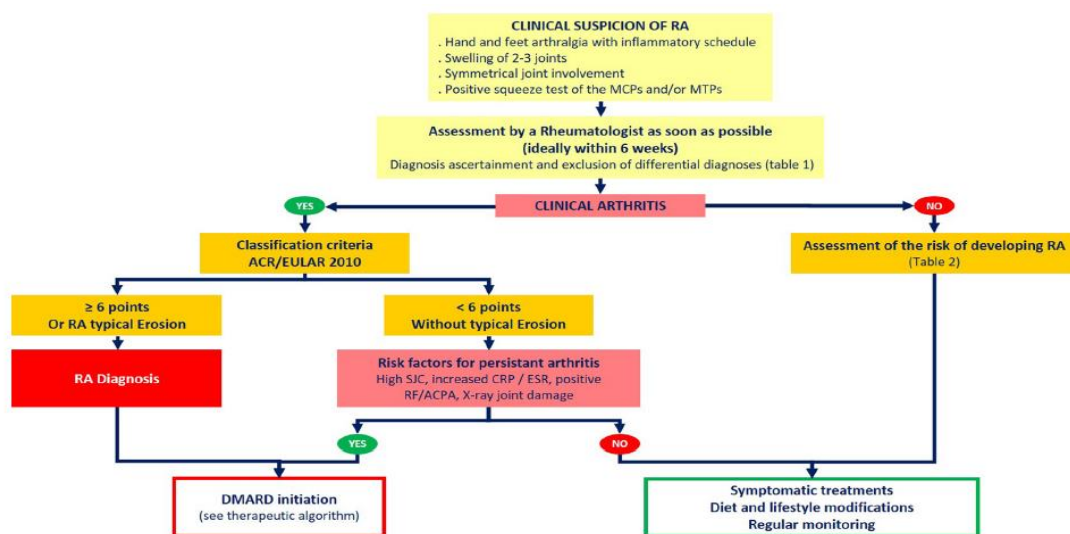


Fig. 1. Diagnostic algorithm for rheumatoid arthritis (RA). RA: rheumatoid arthritis; ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; SJC: swollen joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; DMARD: disease-modifying anti-rheumatic drug; MCP: metacarpophalangeal; MTP: metatarsophalangeal.

The second area concerns clinical presentation (i.e., mainly the items defining clinically suspect arthralgia, proposed by EULAR and validated in several studies) (Supplement 1, Table S1.1). Other less robust clinical elements are presented as supplementary material (Supplement 1, Table S1.2).

Table 1
Minimum work-ups for suspected rheumatoid arthritis.

Clinic	Detailed interview and physical examination
Biology	Blood count Erythrocyte sedimentation rate, C-reactive protein level Transaminase, serum creatinine levels Urine dipstick Rheumatoid factor, anti-citrullinated peptide antibodies (ACPA) Anti-nuclear antibodies
Imaging	Front X-rays of hands and wrists and front X-rays of feet + three-quarter X-rays of all painful joints Chest X-ray or low-dose CT scan

The third area concerns immunological status and the presence of autoantibodies. The value of anti-carbamylated protein antibodies was discussed but was not retained since their detection is not available in current practice (Supplement 1, Tables S1.3 and S1.4) and was put on the research agenda. Notably, the data in the literature do not allow to conclude any benefit in monitoring the persistence and variation of RA-specific autoantibody levels overtime (Supplement 1, Table S1.5). In fact, despite a progressive increase in levels and a spread and diversification of epitope recognition (epitope spreading) in the years preceding the onset of RA[43], the persistence and variation of autoantibody levels in PARRA do not discriminate those in whom RA will develop or not [44, 45].

Table 2
Factors for assessing the risk of rheumatoid arthritis (RA).

Environment	Smoking, occupational exposure , periodontitis, obesity, unbalanced diet, low socio-economic status, sedentary lifestyle, stress, depression, etc.	
Clinic	Clinically suspicious arthralgias if at least 4 of the 7 criteria are met	Symptom duration < 1 year Morning stiffness \geq 1 hr Early-morning pain Localized MCP pain Pain on closing the fist Pain on transverse pressure of the MCP Family history of RA in first-degree relatives
Biology	Number of positive autoantibodies and their level	ACPA (anti-CCP2 or CCP3) Rheumatoid factor (IgA or IgM)
Imaging	Ultrasonography	Synovitis GS \geq 2 or PD+ on wrists, MCP joints 1–5, IPP joints 1–5 or MTP joints 2–5 PD+ tenosynovitis of carpal ulnar extensors, common extensors or finger flexors

MCP: metacarpophalangeal; ACPA: anti-citrullinated protein antibody; IPP: interphalangeal, MTP: metatarsophalangeal; GS: grey scale; PD+: power Doppler positive signal. MRI can help quantify the risk of RA (tenosynovitis in the hands or feet, intermetatarsal bursitis and overall inflammation score associated with increased risk) but is not currently recommended in practice.

Finally, the fourth area concerns imaging (Supplement 1, Tables S1.6, S1.7, and S1.8). Ultrasonography and MRI are 2 use-ful tests for predicting the risk of progression to RA. Nevertheless, their positive and negative predictive values depend above all on the a priori risk and therefore the clinical situation and the physician assessing the risk. Ultrasonography, B-mode and/or Doppler, of wrists, hands and forefeet enables the detection of:

- synovitis on the dorsal surface of the wrist, metacarpophalangeal and interphalangeal joints 1 to 5, and metatarsophalangeal joints 2 to 5;
- tenosynovitis with a positive Doppler signal on the flexor tendons of the fingers, extensor digitorum communis and extensor carpiulnaris;

- the presence of erosions, with Doppler signal, on metacarpophalangeal joints 2 and 5 and metatarsophalangeal joint 5 [46].

It has a positive predictive value ranging from 65% to 85% and a negative predictive value from 24% to 56%. For MRI, the presence of tenosynovitis or intermetatarsal bursitis and the overall inflammation score on MRI may be of interest in predicting the risk of progression to RA [47–49]. Nevertheless, all these abnormalities are also present in healthy individuals, and all studies cited corrected the MRI abnormalities found, excluding those found in more than 5% of healthy individuals of the same age. Because such correction is not feasible in current practice when interpreting an MRI examination, the working group did not want the MRI to appear in the table. In that not all joints of interest can be explored by a single MRI scan and the cost of MRI is much higher than that of ultrasonography, the latter remains the examination of choice in this situation. Notably, assessing and explaining the risk of RA has a positive impact on the individuals concerned, allowing them to feel reassured without aggravating their anxiety [50].

Recommendation 2

As soon as the diagnosis of RA is established or in the presence of risk factors for persistent arthritis, a disease-modifying therapy must be initiated.

In the absence of clinical arthritis, a background treatment to prevent the onset of RA should not be introduced. Management will then primarily rely on symptomatic treatments, hygienic-dietary rules, and monitoring.

(Level of evidence Ia, grade A).

As compared with the previous recommendations, 2 situations were added:

- patients with arthritis and risk factors for persistent arthritis;
- individuals with no clinical arthritis.

In patients with arthritis but not meeting 2010 ACR/EULAR classification criteria (absence of typical radiographic erosion and < 6 points), disease-modifying therapy should be initiated in the presence of one or more risk factors for persistent arthritis (Table 2). This recommendation is in line with the 2016 update of the EULAR recommendations on recent arthritis [8] and the concept of window of opportunity [51]. Nevertheless, most of the studies of patients with recent undifferentiated arthritis were performed before the 2010 ACR/EULAR criteria publication and therefore included many patients not meeting the 1987 ACR criteria but satisfying the 2010 ACR/EULAR criteria (39% in the PROMPT study [52], 63% in DINORA [53], 68% in STREAM [54], 75% in IMPROVED [55] and 95% in tREACH [56]).

For people with no arthritis, no evidence for a differential diagnosis, and several risk factors for progression to RA (ACPA ± clinically suspect arthralgia ± inflammation on MRI), the recommendation was based on the results of 8 randomized controlled trials (RCTs). The inclusion criteria of the trials were heterogeneous (Supplement 1, Tables S1.1–4). The interventions tested were 2 injections of 100 mg dexamethasone at 6-week intervals [57],

hydroxychloroquine (200 to 400 mg/d for 1 year) [58], 1 injection of methylprednisolone 120 mg followed by optimized methotrexate (MTX) 25 mg/week for 1 year [59], abatacept 125 mg/week for 1 year (2 studies) [60,61], rituximab 1 g single dose preceded by 100 mg methylprednisolone [62], atorvastatin 40 mg/d [63] or a program to correct environmental and lifestyle risk factors [64]. GCs, hydroxychloroquine, MTX and statins had no effect on the risk of RA. Rituximab and abatacept had only a suspensive effect during the treatment period, delaying rather than preventing the onset of RA. The effect of these treatments on symptoms was evaluated only with MTX. The use of MTX significantly reduced pain and impact but with an effect that cannot be considered clinically relevant (mean decrease of 0.09/3 in Health Assessment Questionnaire score and decrease of 8/100 in pain score) [59]. As a result, the experts of the working group concluded that none of these treatments can prevent progression to RA and that there is no evidence to date for a symptomatic effect. Therefore, their prescription can-not be recommended, and priority should be given to symptomatic treatment, correction of lifestyle risk factors by hygienic-dietary rules and monitoring. PARRA and their GPs should be aware of the warning signs that require prompt referral to a rheumatologist with the onset of clinical arthritis.

The effect of correcting modifiable risk factors has been assessed in only one RCT evaluating a dedicated program but including a small number of individuals (n = 47) with a short follow-up (4 months), so the results are not robust [64]. Several cohort studies have also examined the impact of smoking cessation on the risk of RA, concluding that the risk is reduced after 10 to 20 years of cessation [65, 66]. Hence, the proposal to correct risk factors to prevent progression to RA is essentially based on expert opinion and has been put forward in the research agenda. Monitoring the risk of RA is recommended over a period of 1 to 3 years (the period most at risk of the development of RA), at a frequency adapted to the level of assessed risk (initially 3 to 12 months) and based primarily on clinical examination. It can then be spaced out. Also, these patients must be educated to recognize the signs that require rapid consultation, specifically the occurrence of joint swelling.

Recommendation 3

The aim of treatment is to achieve and maintain clinical remission or at least low activity, based on validated composite criteria, including joint indices.

(Level of evidence Ia, grade A).

This recommendation combines recommendations 3 (“The aim of treatment is to achieve and maintain clinical remission, or at least low disease activity. Clinical remission is defined by the absence of signs and symptoms of significant inflammatory activity.”) and 4 (“Disease activity should be measured by validated composite criteria, including joint indices.”) of the previous recommendations version. The working group decided to merge the recommendations because they were complementary and corresponded to a single domain. A table showing the definitions of remission and low level of activity with the various validated composite criteria (including the revised 2023 ACR/EULAR definition of Boolean remission [67]) has been added (Table 3).

Table 3
Definitions of remission, low level of activity and minimum improvement required at 3 months using the main validated composite criteria.

Composite criteria	Target (reached at 6 months maximum)		Improvement (interim assessment at 3 months)
	Remission	Low activity	
DAS28-ESR	DAS28-ESR < 2.6	DAS28-ESR 2.6–3.2	Decrease > 1.2 or target achievement
DAS28-CRP	DAS28-CRP < 2.6 ^a	DAS28-CRP 2.6–3.2 ^a	Decrease > 1.2 or target achievement ^a
Boolean remission ACR/EULAR	Original definition: TJC, SJC, Patient global VAS score and CRP level (in mg/dL): all ≤ 1 Revised 2023 definition: same except for VAS score ≤ 2/10		Decrease > 50% in SJC, patient global VAS activity and CRP level or target achievement
SDAI	SDAI ≤ 3.3	SDAI 3.3–11	Decrease > 50% or target achievement
CDAI	CDAI ≤ 2.8	CDAI 2.8–10	Decrease > 50% or target achievement

ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; TJC: tender joint count; VAS: Visual Analog Scale.

^a Thresholds used in practice but not validated [176–178].

Recommendation 4

Therapeutic choice and adaptation must take into account factors other than disease activity, such as structural damage progression, extra-articular manifestations, associated diseases, tolerance and adherence to treatment, and the patient's opinion and feelings.

(Level of evidence Ia/Ib, grade C).

This recommendation was slightly modified, with the addition of extra-articular disorders, specifically referring to pulmonary involvement, and the patient's opinion and feelings proposed by the patient association representatives. The recommendation is a key element of the quality of disease management, particularly in the context of Janus kinase inhibitor (JAKi) alerts. It also paves the way for specific situations, such as pregnancy, scheduled surgery, and travel, which are addressed in extensive detail by the Club Rhumatismes and Inflammation (CRI) fact sheets that are produced and regularly updated by the CRI (<http://www.cri-net.com/>) [68–70].

Recommendation 5

The rheumatologist should monitor the disease closely (1 to 3 months) for as long as it is active.

If there is no improvement within 3 months of starting treatment or if the therapeutic goal has not been reached by 6 months, treatment should be adjusted.

(Level of evidence Ia/IIb, grade B).

This recommendation was not modified, apart from the adjective “frequent”, which was replaced by “close”. This recommendation may represent a challenge in regions with low medical density. The working group decided to define improvement according to the composite index used to quantify RA activity (Table 3). Studies using the Disease Activity Score in 28 joints (DAS28) show a minimum variation of 1.2 points, as defined in the EULAR good response [71,72]. An improvement of 0.6 points (defining partial response) is

potentially insufficient [73] and was not retained by the working group. However, the 1.2-point change is difficult to achieve in patients with initially moderate disease activity; in this case, the therapeutic goal will likely be reached more quickly, potentially as early as 3 months after treatment initiation. For its part, EULAR proposes an improvement of at least 50% in disease activity, based on the study by Aletaha et al., which showed that a 58% improvement at 3 months in Clinical Disease Activity Index (CDAI) or Simple Disease Activity Index (SDAI) is necessary to have reasonable chances to achieve a low level of activity or remission at 6 months [74]. In a similar Japanese study of recent RA patients, a 50% to 60% improvement in the number of swollen joints, C-reactive protein level and patient global assessment at 3 months was required to prevent structural progression at 2 years on DMARDs [75].

Recommendation 6

MTX is the first-line DMARD for patients with active RA, with an initial dosage of at least 15 mg/week, which can be optimized up to 25 to 30 mg/week at 1 to 3 months, depending on patient weight, MTX efficacy and safety.

(Level of evidence Ia, grade A).

As in the previous version of the guidelines, this recommendation confirms the central role of MTX as a first-line treatment. The SLR for the past 2 years identified 3 studies (among 26 evaluating the efficacy of DMARDs) of patients starting RA and who were DMARD-naïve (Supplement 2, Table S2.1.1). A first academic RCT compared the combination of conventional synthetic DMARDs (csDMARDs) with 3 targeted biotherapies, anti-tumor necrosis factor (anti-TNF; certolizumab), anti-interleukin6R (anti-IL-6R; tocilizumab) and cytotoxic T-lymphocyte associated protein 4-immunoglobulin (abatacept) [76]. This study showed the superiority of certolizumab and abatacept over the csDMARD combination (Supplement 2, Table S2.1.2). However, the reference strategy was fixed and maintained for the duration of the trial and did not correspond to the dynamic strategies (step-up or step-down) based on disease activity (treat to target) as recommended by the EULAR and SFR. If these strategies had been applied, inadequate response to csDMARD combination at 3 months would have led to rapid introduction of a targeted therapy with probably no residual difference in disease activity [55, 77]. Two other studies concerned JAK is, with contradictory results [78–81] (Supplement 2, Tables S2.1.2 and S2.1.3). Besides this new evidence, several studies, including the GUEPARD, Be St and IMPROVED trials, as well as the ESPOIR observational cohort, have demonstrated that the introduction of targeted therapy, in these examples TNF inhibitors (TNFis), in patients with early RA was no better than the introduction of anti-TNF agents delayed by a few months if the therapeutic objective was not obtained at 3 to 6 months on first-line csDMARDs used as monotherapy [55, 77, 82–85]. As a result, the expert panel maintained the previous recommendation, without identifying a place for targeted DMARDs in first-line therapy, even in patients identified by matrices as at risk of structural damage progression at 1 year [86]. This position is in line with the latest EULAR recommendations [9].

The working group wanted to emphasize the importance of optimizing the doses of MTX prescribed. According to the literature [87,88], the group defined a minimum recommended dose of 15 mg/week and a maximum recommended dose of 25 to 30 mg/week adapted according to weight (about 0.3 mg/kg) and tolerance. Doses above this maximum may be associated with safety issues, particularly in the digestive tract, and should be reserved for specific situations. Both oral and subcutaneous routes are possible, the choice based on a joint discussion between the rheumatologist and patient. A recent study suggested that taking MTX 25 mg/week in 2 half-doses on the same day, with a 12-hr interval, is associated with better therapeutic response (and similar safety) at week 16 than a single weekly dose, regardless of the endpoint (EULAR good response, ACR20, 50 and 70 response) [89].

The other points developed in the previous recommendations version remain unchanged, notably:

- MTX must be combined with folic acid supplementation of at least 10 mg/week [90,91];

- MTX should be used initially as monotherapy in first-line RA treatment, combined with another csDMARD or targeted bio-logical or synthetic DMARD (tDMARD) relegated to second-line treatment in case of inadequate response [2,9,17,92–98].

Recommendation 7

In cases of contraindication or early intolerance to MTX in DMARD-naïve patients, leflunomide or sulfasalazine are therapeutic alternatives.

(Level of evidence Ia, grade A).

This recommendation was kept broadly unchanged [2]. Leflunomide (10 to 20 mg/d) and sulfasalazine (2 to 3 g/d) have been maintained at the same level of efficacy as MTX. Because of its low clinical efficacy and lack of structural efficacy, hydroxychloroquine is not recommended as first-line treatment [2, 9, 17].

Recommendation 8

In anticipation of the efficacy of a conventional synthetic disease-modifying treatment, the rheumatologist may propose oral or injectable corticosteroid therapy. The corticosteroid therapy should be prescribed at the lowest possible dose for the shortest possible duration, ideally discontinued between 3 and 6 months.

(Level of evidence Ia, grade B).

The role of GC therapy in early RA has been reaffirmed in the 2024 SFR recommendations, as bridging therapy for the first few weeks following the introduction of a first-line DMARD. To make the recommendation simpler and clearer, it now focuses on the notions of low dose and short prescription duration. The working group considered that the

notion of cumulative dose was difficult to grasp at the initiation of GC therapy, so the term was omitted. The use of intravenous or intramuscular bolus of GCs is an alternative, potentially preventing the subsequent prescription of oral GCs, thereby reducing the risk of long-term use. As in the previous version, the working group's experts recognized the clinical and structural efficacy of GC therapy in RA [2,9]. The SLR of recent literature identified 6 articles (4 trials) evaluating the value of GCs of varying nature, dose and duration, in addition to DMARDs (Supplement 2, Table S2.3.1) [99–104]. Three of the studies gave negative results, 2 in terms of disease activity and 1 in terms of quality-adjusted life years, whatever the molecule or dose prescribed (Supplement 2, Table S2.3.1). A randomized placebo-controlled trial (GLORIA) resulted in 3 publications showing a benefit associated with pro-longed low-dose corticosteroid therapy (prednisone 5 mg/d for 2 years) in terms of disease activity according to the DAS28, structural damage progression and use of tDMARDs, with no strong difference in safety except for serious infection compared to the placebo [102–104]. In addition, numerous other publications have shown a dose-dependent association between infectious, cardio-vascular, cutaneous or bone-related adverse effects with as low as 5 to 7.5 mg/d prednisone equivalent [2, 9, 12].

The working group also discussed the position of the latest ACR recommendations, which discourage the use of GC therapy in early RA [105]. The working group felt that this position was too strict because short, low-dose GC therapy is associated with rapid improvement in pain and quality of life in patients at disease onset.

As a result, the experts concluded that the results of the GLORIA trial were of little relevance and maintained the recommendation of low-dose corticosteroid therapy over a short period, which is in-line with the 2023 EULAR recommendations [9]. Of course, certain principles must be respected:

- the prescription of GC therapy, even at low dose and over a short period, must take into account potential contraindications and be based on an assessment of the benefit-risk balance at the patient level;
- the therapy must also be associated with preventive measures to reduce the risk of adverse effects;
- a strategy for tapering and stopping the therapy within 3 to 6 months must be established from GC therapy initiation.

Recommendation 9

In patients with insufficient response or intolerance to MTX (or other first-line csDMARD) and in the absence of poor prognostic factors, rotation or combinations of csDMARD may be proposed.

(Level of evidence V, grade D).

The second-line strategy for patients with inadequate response to MTX or another first-line csDMARD has been broken down into 2 complementary recommendations, stratified according to the presence or absence of poor RA prognostic factors. These factors remain unchanged:

- presence of at least one erosion typical of RA from the outset;
- presence of serum rheumatoid factor or anti-CCP antibodies (ACPA) at high titers ($\geq 3N$)
- moderate to high disease activity despite ongoing csDMARDs, with a high number of swollen joints and/or elevated erythrocyte sedimentation rate or C-reactive protein values;
- failure with ≥ 2 csDMARDs [2,77,86].

The first recommendation for second-line treatment concerns patients with no poor prognostic factors. In the absence of a new publication specifically focused on this RA profile, it adopts the wording of the 2018 recommendations positioning rotation (sulfasalazine, leflunomide) or the combination of csDMARDs (e.g. MTX, sulfasalazine, hydroxychloroquine) at the same level [2]. If there is no response to this second line of csDMARDs, the patient will be considered to have at least one poor prognostic factor (failure of 2csDMARDs) and will be eligible for targeted therapy (recommendation 10). This recommendation is in line with the latest EULAR recommendations [9].

Recommendation 10

In patients with inadequate response to MTX (or other first-line csDMARD) and in the presence of poor prognostic factors, the addition of a biologic or synthetic targeted therapy should be proposed.

The prescription of a JAKi must comply with the dedicated recommendations of the EMA PRAC and the SFR.

(Level of evidence Ib, grade A).

This recommendation is the second part of the second therapeutic line recommendation and is aligned with the 2018 recommendation for RA patients with poor prognostic factors [2]. Of the 26 studies published since the last SLR conducted for the 2023 EULAR recommendations [9], 10 studies were head-to-head trials evaluating a targeted DMARD versus a reference active treatment (csDMARD, combination of csDMARDs, bDMARD or tDMARD) in established RA patients with inadequate response to a csDMARD (Supplement 2, tables S2.1.2 and S2.1.3) [74, 75, 97–104]. These studies do not alter the conclusions of previous recommendations. The only statistically significant results were complementary analyses of a trial of upadacitinib versus adalimumab (SELECT Compare), both combined with MTX; the proportion of patients in CDAI remission was higher and changes in Sharp score were lower in the upadacitinib arms [81, 106, 107].

In terms of safety, the expert discussion largely focused on the results of the ORAL Surveillance trial [108], the alerts issued by the EMA [109] and the US FDA [110] and all subsequent publications [6,111]. In summary, the ORAL Surveillance trial evaluated the efficacy and safety of tofacitinib versus an TNFi in patients with active RA despite MTX treatment and with a high-risk cardiovascular profile (age ≥ 50 years and at least one cardiovascular risk factor among active smoking, arterial hypertension, dyslipidemia, diabetes, family history of early coronary artery disease, personal history of coronary artery disease and RA-related extra-articular involvement). This initial study, already incorporated

into the 2023 EULAR recommendations, identified an association of excess of major cardiovascular events (hazard ratio [HR] 1.33 [95%CI 0.91–1.94]) and cancers (HR 1.48 [95% CI 1.04–2.09]) [9,10]. Since then, the SLR performed as part of this update (Supplement 2, Tables S2.2.1, S2.2.2, S2.2.3, S2.2.4, S2.2.5) identified additional analyses of the ORAL Surveillance study: a significant excess risk was identified for severe infections (10 mg × 2/d dose) and herpes infections (all doses) [112], neoplasia (all types) and non-melanoma skin carcinoma (all doses) [113]. In parallel with this trial, several pharmaco-epidemiological studies of registry or insurance data did not confirm this risk excess [114,115]. Of note, pharmaco-epidemiological studies are more sensitive to residual confounding factors than randomized trials (e.g., ORAL Surveillance); specifically, indication bias may reduce the ability to identify a statistically significant excess risk. Also, data from the German RABBIT registry were reported at the 2023 ACR meeting after the guideline development meetings: in this pharmaco-epidemiological study, the risk of cancer (all types) was higher with JAKi than TNFi (HR 1.45 [95% CI 1.0–2.1]), at the limit of statistical significance. When analyses were conducted in patients with the profile of those in the ORAL Surveillance trial, this risk became significant (HR 1.73 [95% CI 1.1–2.73]) [116].

All these factors point to a specific risk profile for JAKis. This led the SFR to issue a first consensus on the management (assessment and preventive treatment) of the risk of cardiovascular and thromboembolic events with JAKis [6]. A second consensus study on the management of neoplastic risk is under way, the results of which will be published in 2024–2025.

On the basis of these data, the panel considered that:

- there were no robust data to conclude that one bDMARD was more efficacious than another, positioning them in the same line in the event of an inadequate response to one (or more) csD-MARDs;
- although 2 JAKis demonstrated efficacy superior to adalimumab and one to abatacept [117–119], the benefit–risk balance of JAKis does not allow them to be positioned ahead of other targeted therapies.

The choice and prescription of targeted therapy should be based on RA disease activity and patient profile (age, previous history, comorbidities, plans to have children). In the presence of cardio-vascular risk factors, the recommendations of the PRAC and the SFR consensus (Fig. 2) should be followed, and JAKis should be considered only if there is no therapeutic alternative. Targeted therapies that have demonstrated cardiovascular benefit (TNFis and IL-6Ri) should be preferred. In the presence of a history of cancer, the rheumatologist may refer to the 2023 EULAR recommendations [120]; rituximab is preferred with a history of hemopathy, whereas anti-cytokine antibodies (IL-6Ri in particular) are preferred with a history of solid cancer. In this situation, abatacept and JAKis should be considered only if there is no therapeutic alternative. Finally, in the case of present or planned childbearing, certolizumab is preferred because it does not pass into the fetus or into milk [121, 122]. All other special situations are discussed in detail in the CRI factsheets (www.cri-net.com).

Recommendation 11

All targeted therapies (biological or synthetic) should preferably be used in combination with MTX (or leflunomide in case of contraindication to MTX).

(Level of evidence Ia/Ib, grade A).

This recommendation has not been modified from the previous version of the SFR recommendations and is consistent with the 2023 EULAR recommendations [2,9]. There are no recent data to contradict it. It is also aligned with the principle of making therapeutic adjustments sequentially so as to be able to accurately judge the impact of therapeutic adjustment in terms of efficacy or tolerance (and therefore not to stop a partially effective csDMARD at the same time as introducing a tDMARD). MTX and leflunomide are the csDMARDs with the highest level of evidence, with equivalence of efficacy between the 2 molecules when used in combination with a tDMARD [2, 123, 124].

In the event of safety issues, a reduction in MTX dosage may be discussed as part of a shared decision involving the patient, respecting the minimum dosage of 10 mg/week [2, 88, 125].

Finally, in cases of contraindication to MTX or leflunomide, anti-IL-6R antibodies and JAKis should be preferred because they have a label to be used as monotherapy.

Recommendation 12

Patients with failure of a targeted DMARD (biological or synthetic) should receive another targeted DMARD.

The prescription of a JAKi must comply with the dedicated recommendations of the PRAC and the SFR.

(Level of evidence Ia/V, grade D).

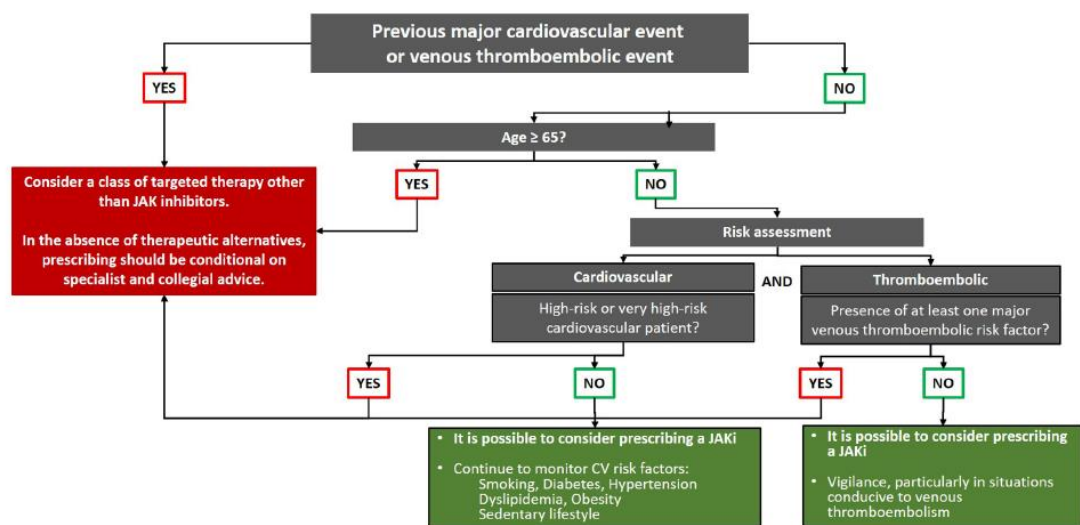


Fig. 2. Assessment of cardiovascular risk according to the work of the Société française de rhumatologie (SFR) consensus group (and the European Medicine Agency's Pharmacovigilance Risk Assessment Committee [PRAC]) [6]. JAKi: Janus kinase inhibitor; CV: cardiovascular.

The principle of this recommendation was not modified and remains aligned with the 2023 EULAR recommendations [2,9]. However, it has been simplified to leave as many therapeutic options as possible. Specifically, the recommendation to change the mode of action in the event of primary failure has been removed because although some studies have shown a lower response rate to a second tDMARD with the same mechanism of action [2, 126–128], a significant number of patients may still show adequate response to such an option. This decision is partly in line with the 2023 EULAR recommendations, which specify that the use of a second TNFi or a second anti-IL-6R antibody is possible after failure of a first one [9]. The expert group considers that this recommendation can also apply to JAKis. However, failure of 2 DMARDs blocking the same pathogenic pathway should lead to prescription of a drug with a change of mode of action.

As a result, all details have been removed from the recommendation, leaving the rheumatologist to decide on the best therapeutic option according to the patient profile and disease characteristics, as part of a shared decision with the patient. Obviously, as in recommendation 9, the choice of a JAKi must comply with PRAC and SFR recommendations [6].

Recently, the concept of difficult-to-treat RA has been proposed by a working group of EULAR [129]. It was based on 3 criteria:

- failure of at least 2 tDMARDs with different mechanisms of action;
- presence of at least one sign of disease activity among at least moderate RA activity, symptoms suggestive of active disease, inability to reduce GC therapy, rapid radiographic progression, and symptoms impairing quality of life
- management perceived as problematic for the rheumatologist or patient.

The concept was associated with a proposed management strategy, which, depending on the circumstances, could include reassessment of the diagnosis, assessment of comorbidities that might interfere with RA disease activity, suboptimal therapeutic compliance, initiation of non-drug therapies to manage non-inflammatory symptoms, or therapeutic escalation [130].

Recommendation 13

In the event of persistent remission without GCs, a gradual DMARD (conventional synthetic or targeted) reduction should be considered.

(Level of evidence IIb/IV, grade C).

This recommendation was modified since the 2018 SFR recommendations and is aligned with the 2023 EULAR recommendations [2,9]. Numerous studies have shown a real risk of overtreatment in patients with RA in persistent remission (i.e., maintained over at least 6 months) because the DMARD dosage required to maintain remission is probably lower than that needed to achieve remission in active RA. Therefore, the idea is to identify the minimum effective dose for this maintenance [131–133]. This situation has led the group to change the wording from “may” (2018) to “should” be considered (2024). In the 2016 EULAR update, tapering was recommended in 2 stages, starting with tapering (to eventual discontinuation) of the tDMARD, followed by tapering (to eventual

discontinuation) of the csDMARD. More recent publications [9] (Supplement 2, Table S2.1.5) have shown that tDMARD tapering may lead to greater risk of relapse than csDMARD tapering, without major difference in costs. As a result, the group considered that if the objective of avoiding over-treatment was paramount, the choice of the molecule to be tapered or discontinued could be left to the rheumatologist, as part of a shared decision with the patient. Therapeutic tapering can be achieved by reducing the dosage if several doses are available or by spacing out intakes. Finally, the group of experts considers that over-treatment prevention aims to identify the lowest efficacious DMARD posology and is not equivalent to drug discontinuation (“therapeutic vacations”), given the risk of relapse. Thus, all trials that have tested tapering strategies show that only 10% to 15% of patients at most are able to maintain treatment-free remission in the medium term [84, 134–137]. In this respect, in the event of a loss of remission (i.e., a relapse of RA), re-introducing or re-increasing the dose to the lowest efficacious dose (i.e., the previous dose with which remission was maintained) of a tDMARD or csDMARD enables remission to be achieved again in 80% to 90% of patients [9].

The overall therapeutic strategy is summarized in Fig. 3.

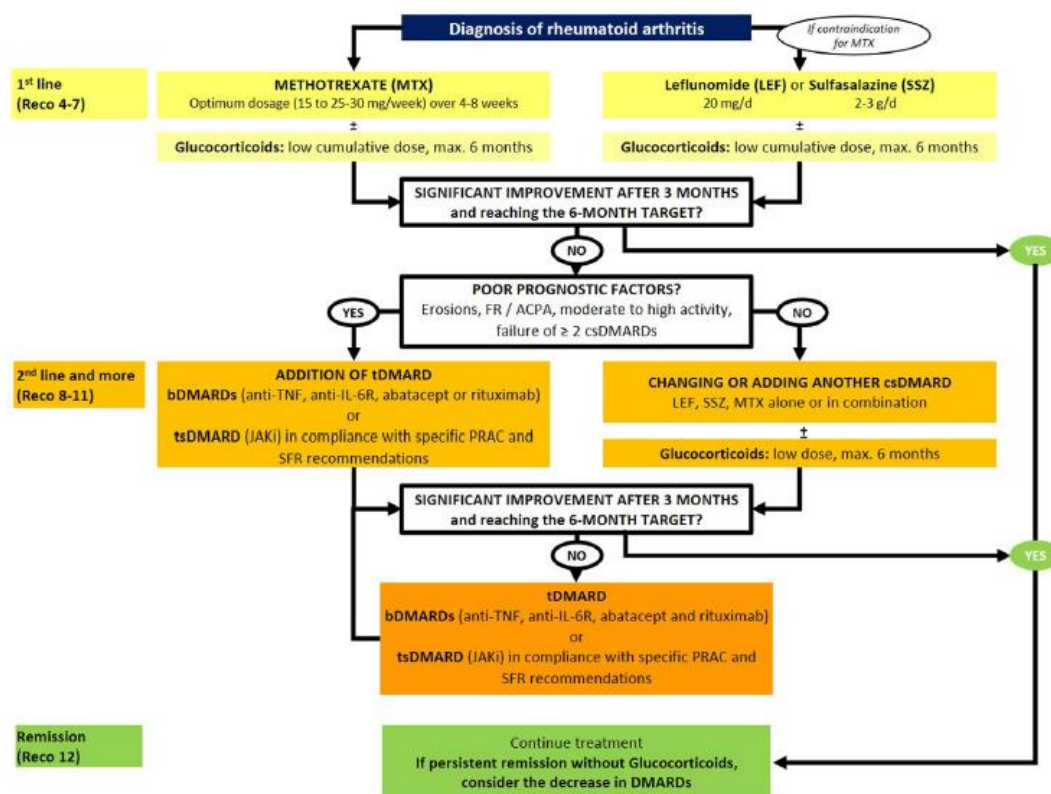


Fig. 3. Decision tree for the therapeutic management of rheumatoid arthritis; bDMARD: biologic disease-modifying anti-rheumatid drug; tDMARD: targeted disease-modifying anti-rheumatid drug; TNF: tumor necrosis factor; IL: interleukin; JAKi: Janus kinase inhibitor; PRAC: European Medicine Agency’s Pharmacovigilance Risk Assessment Committee; SFR: Société française de rhumatologie.

Recommendation 14

Co-morbidities and their risk factors should be screened and assessed periodically and their management coordinated.

Care must be combined with lifestyle advice (regular physical activity, smoking cessation, balanced diet, etc.) and updating of vaccinations.

(Level of evidence IIb/IV, grade C).

This recommendation remains unchanged, and the importance of identifying and managing comorbidities through drug and non-drug intervention has been reaffirmed. This is the responsibility of both the rheumatologist and the GP. The frequency of assessment has deliberately not been specified because this is based on few data and depends on both the depth of the proposed assessment and the level of risk identified. As proposed by the EULAR, cardio-vascular risk assessment should be performed at least every 5 years. Since 2018, the SFR has produced specific recommendations on diet [138].

The working group discussed the relevance of adding patient education to this recommendation. Therapeutic education, whether delivered by healthcare professionals or members of patient associations, already has a major role in the management of RA, and this was clearly stated in the general principles. For this reason, the group decided not to include it in this recommendation. The overall picture is summarized in Fig. 4.

Recommendation 15
 The rheumatologist should systematically investigate symptoms and physical signs associated with pulmonary involvement (chronic cough, dyspnea, pulmonary auscultation abnormalities, digital hippocratism, etc.) at diagnosis and during follow-up of RA patients.
 (Level of evidence V, grade D).

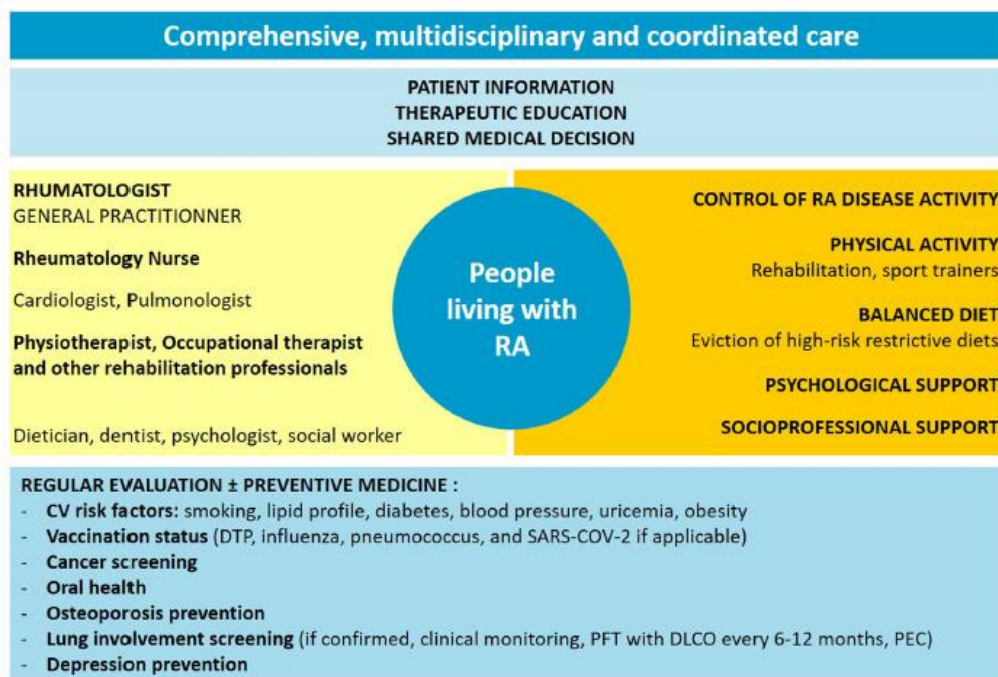


Fig. 4. Principle of patient-centered, multidisciplinary care.

The first recommendation concerning RA-ILD focuses on the diagnosis of pulmonary involvement. RA-ILD is a heterogeneous entity, usually diagnosed within the first 10 years of the evolution of RA but sometimes preceding it [139]. Acute or sub-acute forms exist but are rare, and most patients present a slowly progressive form [140]. This situation explains why the diagnosis of ILD is often delayed. The first symptom is usually exertional dyspnea, which may be discreet in patients with reduced physical activity due to rheumatic disease. For this

reason, the diagnosis should be sought by means of an interview focusing on dyspnea in daily life activities, the search for chronic cough with or without sputum, clinical examination looking for auscultation abnormalities and digital hippocratism. These clinical signs are neither sensitive nor specific and may be due to other respiratory diseases associated with RA (emphysema, bronchiolitis, bronchial dilatation, pleural damage, etc.) [141]. These are outside the scope of these 2024 recommendations.

Several factors associated with the occurrence of ILD during RA have been identified: male sex, late age of onset of RA, current or past heavy smoking, obesity, high ACPA positivity and high RA disease activity [142–145]. In addition, inhaled environmental riskfactors (industrial pollution, silica, etc.) may increase the risk of RA-ILD.

Recommendation 16

In the presence of respiratory symptoms and/or physical signs, a high-resolution thoracic CT scan with thin sections should be performed.

In the absence of respiratory symptoms and/or physical signs, routine screening for interstitial lung disease (ILD) using high-resolution chest CT is not currently recommended.

(Level of evidence III, grade D).

This recommendation guides the rheumatologist in 2 distinct approaches.

The first is a diagnostic approach in a symptomatic patient. Chest X-rays and pulmonary function tests (PFTs) are not sensitive and cannot be used to diagnose incipient ILD. High-resolution chest CT(HR-CT) is the reference examination recommended by the learned pulmonology societies for the diagnosis of idiopathic pulmonary fibrosis in autoimmune diseases [146]. Thoracic HR-CT can also be used to point out the characteristics of the interstitial involvement and measure its extension. Usual interstitial pneumonia (UIP) and non-specific interstitial lung disease (NSIP) are the most frequent presentations, with poorer prognosis associated with NSIP than UIP, which will have therapeutic implications (see Recommendations 18 and 19). Thoracic HR-CT can also be used to rule out differential diagnoses of RA-ILD. Other examinations should be performed to assess the impact of ILD. PFTs are used to assess the functional impact of ILD: reduced slow diffusion capacity of lungs for carbon monoxide (DLCO < 70% of theoretical) and/or restrictive disorders (total lung capacity < 80% of theoretical). DLCO and forced vital capacity (FVC) are also associated with the prognosis of RA-ILD. The 6-min walk test, which objectively assesses hypoxemia and dyspnea on exertion, can be proposed, but the interpretation of results must take into account the patient's functional capabilities. Trans-thoracic echocardiography can help in the diagnosis of dyspnea by ruling out left-sided heart failure or primary/secondary pulmonary hypertension.

The second approach corresponds to a systematic screening approach for asymptomatic patients at risk of ILD. The working group decided against the implementation of systematic screening for RA-ILD. RA-ILD does not meet the screening criteria established by the World Health Organization (WHO), which require a high level of proof of the benefit of therapeutic intervention (i.e., its ability to reduce the incidence of the disease or improve its prognosis [147]). At present, no studies are available on the possible benefit of early therapeutic intervention. Approximately half of patients with RA-ILD have stable disease with no

indication for specific treatment [140]. Only initial scanographic extension has been identified as associated with functional progression of RA-ILD[148–150]. Finally, with the exception of nintedanib, the level of evidence to justify the initiation of treatment in progressive RA-ILD is very low.

The working group studied alternatives to chest HR-CT for detecting RA-ILD. The various tools currently proposed are PFTs, lung ultrasonography and the electronic stethoscope. In the case of PFTs, studies have shown insufficient sensitivity for detecting incipient ILD [151,152]. Pulmonary ultrasonography has recently been developed for evaluating ILD associated with systemic autoimmune diseases [153] Its performance seems of interest in cases of established ILD but needs to be confirmed in screening situations. Finally, the electronic stethoscope has been the subject of only one publication, the results of which need to be confirmed [151].

Recommendation 17

RA-ILD in a patient should be managed in collaboration with an expert pulmonologist.

All patients with RA-ILD should be followed up with at least (1) a check for the onset or worsening of respiratory symptoms and physical signs at each consultation and (2) pulmonary function tests, including DLCO measurement of DLCO, every 6 to 12 months.

All patients with RA-ILD should be made aware of symptoms suggesting worsening pulmonary disease.

(Level of evidence V, grade D).

For these first recommendations on the management of RA-ILD, the working group stressed the importance of multidisciplinary management, highlighting the benefits of collaboration between the rheumatologist and a pulmonologist or an expert pulmonology center. The role of the treating rheumatologist will be central to the assessment of pulmonary clinical signs throughout the follow-up because the progression of respiratory disease may be reflected in the appearance and/or increase in pulmonary clinical signs. Of course, as with any RA, smoking cessation and vaccinations against influenza, pneumococcus and SARS-CoV-2 are strongly recommended because the presence of ILD is a risk factor for severe forms of pulmonary infection. The same applies to the prescription of adapted physical activities, with the possibility of respiratory rehabilitation in the event of maladaptation to exertion. Also, patients with RA-ILD must be educated to recognize the clinical signs of lung damage themselves, with a view to self-monitoring. In the case of established ILD, the expert pulmonologist must determine the exact modalities of follow-up (frequency of re-evaluation of PFTs and HR-CT), particularly in cases of immediately severe ILD or the presence of poor prognostic factors. In the literature, apart from the usual factors such as age, male sex or active smoking, the factors associated with mortality or progression of ILD are low initial FVC and DLCO values, appearance of UIP, initial extension of ILD and extent of fibrosis on HR-CT [154,155]. The working group wanted to insist on non-invasive follow-up of all RA-ILD patients, including PFTs every 6 to 12 months, to monitor changes in FVC and DLCO. In the event of deterioration in clinical and/or functional parameters, a thoracic HR-CT may be requested, in agreement with the pulmonologist, to quantify the radiographic progression of ILD.

Therefore, the working group considered that recommendations could not be issued on the specific therapeutic management of ILD. The current level of evidence in the literature concerning the specific therapeutic management of RA-ILD is low. The only 2 randomized trials available concern the evaluation of 2 anti-fibrotic agents: nintedanib and pirfenidone. For nintedanib, the randomized placebo-controlled INBUILD trial included 663 patients with progressive fibrosing ILD, including 89 with RA-ILD [156]. In this specific population, nintedanib slowed FVC loss with an annual difference of 117.9 mL (95% CI: 5.2–230.7) [157]. For pirfenidone, the TRAIL 1 trial included 123 patients with fibrotic RA-ILD, with no progression criteria [158]. This study gave negative results on the primary endpoint (a composite endpoint including death and > 10% decline in FVC at 52 weeks), but the decline in FVC at week 52 (secondary endpoint corresponding to the primary endpoint of the INBUILD study) was significantly reduced in UIP with an annual difference of 126 mL ± 39 (P = 0.01). The tolerability of antifibrotic agents was poor overall, with digestive, hepatic or cutaneous side effects, responsible for suboptimal therapeutic maintenance in the trials (19.6% discontinuation at 1 year for nintedanib and 24% for pirfenidone) [156,158]. These results were confirmed by another retrospective study [159].

The SLR on the role of immunosuppressive agents in RA-ILD treatment mainly identified a recent retrospective study including 212 patients with RA-ILD. It suggests that mycophenolate mofetil, azathioprine or rituximab may decrease the modeled slope of decline in FVC and DLCO, regardless of scanographic appearance (UIP or non-UIP) at 12 months [160]. Specific forms of inflammatory RA-ILD, such as organized lung disease or lymphocytic ILD, could benefit from immunosuppressive therapy, alone or combined with GCs.

These elements indicate that the use of an antifibrotic or immunosuppressive agent in RA-ILD can only be determined on a case-by-case basis after multidisciplinary discussion with an expert pulmonologist.

Recommendation 18

In RA patients with ILD, initiation or continuation of MTX therapy is possible.

(Level of evidence IIIc, grade C).

In a cohort study of US veterans with RA-ILD, high RA activity assessed by mean DAS28 during follow-up was associated with mortality [161]. Despite no studies demonstrating the beneficial impact of RA control on the progression of ILD, several studies have identified an association between high disease activity (i.e., elevated DAS28) and risk of ILD during RA [142,143]. These findings suggest that control of RA activity may have an impact on pulmonary prognosis.

MTX has long been incriminated as a risk factor for RA-ILD onset and therefore has frequently been discontinued by pulmonologists and/or rheumatologists as soon as ILD is diagnosed in a patient with RA. With MTX as the cornerstone of RA treatment, the working group wanted to assess the use of MTX in RA-ILD in light of recent literature. Drug-related immunoallergic pneumonia, which mainly occurs in the first year of a treatment, is rarely linked to MTX and remains an exclusion diagnosis. Using different statistical methods (cohort study, retrospective multicenter case-control study, pharmacoepidemiological studies based

on national health data), several recent studies have not identified any positive association between MTX and the risk of RA-ILD [162–164]. Some even suggest a potentially beneficial effect of MTX, preventing or delaying the onset of ILD [162,163]. In addition, most studies report no negative impact or even a potential beneficial effect of MTX on mortality in patients with RA-ILD [165,166]. Therefore, there is no reason to systematically contraindicate the use of MTX in patients with RA-ILD. In the case of established and severe ILD, the appropriateness of MTX treatment should be the subject of a multidisciplinary discussion with an expert pulmonologist. If there is any doubt about MTX-related immunoallergic pneumonitis (an acute or sub-acute clinical picture without any other cause, particularly infectious, with improvement on discontinuation of MTX), the responsibility of MTX should be systematically discussed with an expert pulmonology center. The same rule applies to other potentially pneumotoxic drugs.

Recommendation 19

When a tDMARD is needed in a patient with RA-ILD, abatacept or rituximab should be used.

(Level of evidence IIIc, grade C).

With regard to tDMARDs, a few studies have described excess mortality in patients with RA-ILD treated with TNFis, raising doubts about the benefit–risk balance of this therapeutic class in such patients [167, 168]. However, these studies are fraught with bias, and the use of TNFis in RA-ILD needs to be re-evaluated in light of scientific works currently in progress.

For the other modes of action, a Spanish registry study showed stability of FVC and DLCO after a median follow-up of 12 months (interquartile range 6-36) in 263 RA-ILD patients, with overall not very severe disease, initiating abatacept; scanographic worsening was identified in only 23.4% of patients [169]. Rituximab has been the subject of positive therapeutic trials in ILD associated with other autoimmune diseases [170, 171]. In addition, 4 uncontrolled studies of specifically patients with RA-ILD (n = 133) demonstrated an improvement in FVC and DCLO after initiation of rituximab [172–174]. Data on tocilizumab and JAKis are currently poor. Of note, male sex, age and smoking status are common risk factors for RA-ILD and the excess cardiovascular and neoplastic risk reported with JAKis. No robust data are available for other DMARDs.

All recommendations with their related percentages and level of agreements are in Table 4. The items on the research agenda are summarized in Table 5.4.

Discussion

This new version of the French SFR recommendations on the diagnosis and management of RA is intended to be an important milestone in optimizing RA care for several reasons. First, the recommendations are published 6 years after the previous version, a rather long time for recommendations [3], especially for a disease for which therapeutic innovations and scientific publications have been numerous over the period. Above all, during this period, the ORAL Surveillance study [108,113] led the US and European drug agencies to issue an alert on the safe use of JAKis, resulting in restrictions on their use in at-risk populations [109, 110]. Several observational studies using data from registry or insurance databases provided

reassuring evidence but did not cancel out the alert. For this reason, it seemed particularly important to integrate all these scientific data in a clear and operational manner into these recommendations, whose aim is to help rheumatologists in usual clinical practice optimally care for their patients. Finally, as with the previous version, these recommendations have been developed with the active participation of patients representing the 2 main associations of people living with RA in France: AFPric (<https://www.polyarthrite.org/>) and ANDAR(<https://www.polyarthrite-andar.org/>). This is an important point because it reflects the commitment of the SFR and its members to give patient partners an important place at all levels of the guideline development process.

As compared with the previous version, the 2024 SFR recommendations reiterate the general principles and general management strategy in terms of diagnosis, follow-up organization and therapeutic choices, without major changes. For JAKis, the current version incorporates data from recent scientific publications and the PRAC, which has led to the clear identification of patients for whom this therapeutic class has a less favorable safety profile than other classes of targeted therapy. Hence, older individuals and smokers, with marked cardiovascular or neoplastic risk factors, are the only patients for whom the prescription of JAKis should be considered in the absence of therapeutic alternatives, after having transparently informed patients of the current state of knowledge on the safety of this therapeutic class. These recommendations are based on a previous SFR consensus and recommendation on cardiovascular risk management in patients with inflammatory rheumatism [6]. Further work is in progress on neoplastic risk management and should be incorporated into the next version of these recommendations.

Two important points have been addressed for the first time in these recommendations: the management of risk of RA in symptomatic people and the management of ILD associated with RA. For the first point, this decision was based on rheumatologists regularly seeing in practice people with various degrees of suspected RA, notably with joint pain or serum ACPAs in a family context of RA. A substantial number of scientific works have been published on this topic in recent years, which led the working group to include this issue in the SLR. The available data have enabled us to better characterize the generally low risk of RA in such a context, although precisely assessing this risk is impossible. The data have also shown that these patients should receive treatment for RA because no DMARD has yet proved its worth in this situation. Rather than making a specific recommendation, the group integrated these points into existing recommendations.

With regard to the second point on RA-ILD, the group considered that this was an issue that regularly presents difficulties for rheumatologists and patients. A great deal of scientific data is already available, and a joint recommendation by pulmonologists and rheumatologists has been in the pipeline for several years. As a result, the working group felt that recommendations should be formulated for rheumatologists, to provide a framework for the investigation and management of RA-ILD. Therefore, 4 recommendations have been formulated, enabling rheumatologists to deal with this potentially severe extra-articular condition and to prepare for the necessary interaction with the expert pulmonologist. Future joint recommendations, rheumatology and pulmonology, focusing on RA-ILD could undoubtedly be easily articulated with our proposals. Several questions could not be resolved by the SLRs and have logically been placed on the research agenda (Table 5).

Finally, all recommendations must lead to an implementation strategy for people with RA and the professionals caring for them [175]. The SFR has already been very effective in

disseminating previous versions of the recommendations via presentations at national and regional congresses. This version of the recommendations was presented at the Congrès national de rhumatologie in Paris in December 2023. In addition, a Continuing Professional Development (CPD) program is being developed by the Conseil national professionnel (CNP) de rhumatologie, to be validated by the Agence nationale de développement professionnel continu (ANDPC). This program is initially based on a clinical audit and has defined a number of quality indicators to identify the penetration of the recommendations in current practice: knowledge of risk factors for the development of RA, proportion of patients with RA onset and initiating disease-modifying therapy within 3 months of the onset of symptoms that led to the diagnosis, proportion of patients screened for comorbidities, proportion of patients identified as being at cardiovascular or neoplastic risk, proportion of consultations during which RA activity is quantified using a composite index, and adequate screening for RA-ILD.

In conclusion, these recommendations provide rheumatologists and patients with a vision of the optimal diagnostic and therapeutic management of RA. An update should be considered within 2 to 3 years.

Table 4
Summary of general principles and recommendations.

		Working group		Reading group
		Agreement (%)	LoA (0-10) Mean ± SD	LoA (%)
	General principles			
A	The management of RA or clinical suspicion of RA requires collaboration between the patient and the rheumatologist, within the framework of shared medical decision-making based on patient information and education	85	9.76 ± 0.60	97
B	The rheumatologist is the specialist who should manage RA or clinical suspicion of RA. The general practitioner plays an important role in detecting the disease and monitoring the patient in coordination with the rheumatologist	85	9.88 ± 0.44	97
C	Any person with RA or clinical suspicion of RA should benefit from comprehensive, patient-centered drug and non-drug management	85	9.52 ± 0.92	95
D	To optimize the overall management of RA, the rheumatologist must take into account the costs associated with RA and its consequences	81	8.88 ± 1.39	81
	Recommendations			
1	The diagnosis of RA requires the presence of at least one clinical arthritis and should be confirmed as soon as possible by the rheumatologist	85	9.40 ± 0.87	94
	If case of suspected RA without any clinical arthritis, the risk of progression to RA should be assessed on the basis of clinical, immunological and imaging criteria			
2	As soon as the diagnosis of RA is established or in the presence of risk factors for persistent arthritis, a disease-modifying therapy must be initiated	85	9.32 ± 0.99	82
	In the absence of clinical arthritis, a background treatment to prevent the onset of RA should not be introduced. Management will then primarily rely on symptomatic treatments, hygienic-dietary rules, and monitoring			
3	The aim of treatment is to achieve and maintain clinical remission or at least low activity, based on validated composite criteria, including joint indices	85	9.68 ± 0.69	97
4	Therapeutic choice and adaptation must take into account factors other than disease activity, such as structural damage progression, extra-articular manifestations, associated diseases, tolerance and adherence to treatment, and the patient's opinion and feelings	85	9.72 ± 0.54	96
5	The rheumatologist should monitor the disease closely (1 to 3 months) for as long as it is active	85	9.36 ± 0.95	93
	If there is no improvement within 3 months of starting treatment or if the therapeutic goal has not been reached by 6 months, treatment should be adjusted			
6	MTX is the first-line DMARD for patients with active RA, with an initial dosage of at least 15 mg/week, which can be optimized up to 25 to 30 mg/week at 1 to 3 months, depending on patient weight, MTX efficacy and safety	85	9.48 ± 0.96	89
7	In cases of contraindication or early intolerance to MTX in DMARD-naïve patients, leflunomide or sulfasalazine are therapeutic alternatives.	85	9.33 ± 1.05	90
8	In anticipation of the efficacy of a conventional synthetic disease-modifying treatment, the rheumatologist may propose oral or injectable corticosteroid therapy. The corticosteroid therapy should be prescribed at the lowest possible dose for the shortest possible duration, ideally discontinued between 3 and 6 months	85	9.33 ± 1.20	97
9	In patients with insufficient response or intolerance to MTX (or other first-line csDMARD), and in the absence of poor prognostic factors, rotation or combination of csDMARD may be proposed	85	9.17 ± 1.01	92
10	In patients with an inadequate response to MTX (or other first-line csDMARD) and in the presence of poor prognostic factors, the addition of a biologic or synthetic targeted therapy should be proposed	85	9.71 ± 0.55	93
11	The prescription of a JAKi must comply with the dedicated recommendations of the PRAC and SFR	85	9.25 ± 0.94	94
	All targeted therapies (biologic or synthetic) should preferably be used in combination with MTX (or leflunomide in case of contraindication to MTX)			
12	Patients with failure of a targeted DMARD (biologic or synthetic) should be treated with another targeted DMARD	85	9.46 ± 0.88	88
13	The prescription of a JAKi must comply with the dedicated recommendations of the PRAC and the SFR	85	9.42 ± 1.32	92
	In the event of persistent remission without glucocorticoids, a gradual DMARD (conventional synthetic or targeted) reduction should be considered			
14	Co-morbidities and their risk factors should be screened and assessed periodically and their management coordinated	85	9.68 ± 0.56	94
	Care must be combined with lifestyle advice (regular physical activity, smoking cessation, balanced diet, etc.) and updating of vaccinations			

15	The rheumatologist should systematically investigate symptoms and physical signs associated with pulmonary involvement (chronic cough, dyspnea, pulmonary auscultation abnormalities, digital hippocratism, etc.) at diagnosis and during follow-up of RA patients	85	9.52 ± 0.71	95
16	In the presence of respiratory symptoms and/or physical signs, a high-resolution thoracic CT scan with thin sections should be performed In the absence of respiratory symptoms and/or physical signs, routine screening for ILD using high-resolution chest CT is not currently recommended	85	9.67 ± 0.64	95
17	The management of RA-ILD should be in collaboration with an expert pulmonologist All patients with RA-ILD should be followed up with at least (1) a check for the onset or worsening of respiratory symptoms and physical signs at each consultation, and (2) pulmonary function tests, including measurement of the limiting DLCO, every 6 to 12 months	85	9.48 ± 0.65	95
18	All patients with RA-ILD should be made aware of symptoms suggesting worsening pulmonary disease	85	9.71 ± 0.55	96
19	In RA patients with RA-ILD, initiation or continuation of MTX therapy is possible When a tDMARD is needed in a patient with RA-ILD, it is preferable to use abatacept or rituximab	85	8.96 ± 1.20	96

DLCO: diffusion capacity of lungs for carbon monoxide; DMARD: disease-modifying anti-rheumatoid drug; csDMARD: conventional synthetic disease-modifying anti-rheumatoid drug; tDMARD: targeted disease-modifying anti-rheumatoid drug; ILD: interstitial lung disease; JAKi: Janus kinase inhibitor; LoA: level of agreement; MTX: methotrexate; PRAC: European Medicine Agency's Pharmacovigilance Risk Assessment Committee; RA: rheumatoid arthritis; SRF: Société française de rhumatologie. The working group's level of agreement is based on the substance of the recommendation, whereas that of the reading group is based on its comprehensibility and practical relevance.

Table 5
Research agenda.

1	Clarify the role of carbamylated protein antibodies for assessing the risk of RA in at-risk individuals
2	Develop algorithms to predict the risk of RA
3	Assess the value of correcting modifiable environmental risk factors to prevent RA in at-risk individuals
4	Identify predictors of treatment response, enabling a personalized therapeutic approach
5	Establish predictors of persistent remission when conventional or targeted DMARDs are discontinued
6	Determine any increased neoplastic risk with Janus kinase inhibitors
7	Identify innovative therapeutics to block the pathogenic process in people at risk of RA
8	Determine the optimal interstitial lung disease screening strategy (modalities and timing)
9	Evaluate the possibility of combining targeted DMARDs in difficult-to-treat RA
10	Evaluate the impact of DMARDs for RA in the evolution of ILD

RA: rheumatoid arthritis; DMARD: disease-modifying anti-rheumatic drug.

Disclosure of interest (personal consulting fees, grants to an institution or employment)

Financial interests

1. Holder of shares, bonds, or other equity financial assets.

Long-term or permanent links

2. Personal remuneration for research activities, scientific evaluation, or consulting.
3. Owner, executive, partner, employee, participation in a decision-making body.
4. Consultant, member of an expert group, or equivalent.
5. Research contract or grant.
6. Research fellowship.

One-time interventions

7. Clinical trials, preclinical trials, and scientific works, as the principal investigator of a single-center study, coordinating investigator, or principal experimenter

8. Clinical trials, preclinical trials, and scientific works, as a co-investigator, non-principal experimenter.

9. Expert reports or writing of promotional articles.

10. Consulting activities.

11. Training activities as a speaker at congresses, conferences, symposiums, various public meetings.

Indirect interests

12. Payments to the budget of an institution for which you are responsible.

13. Close relatives who are employees or have financial interests.

14. Other facts or interests that could be considered detrimental to your impartiality (specify).

BF: AbbVie^{4,5,7,10,11}, Amgen¹¹, Biogen^{4,7,10,11}, BMS^{4,7,10,11}, Celltrion^{4, 10, 11}, Chugai^{4, 7, 10, 11}, Fresenius Kabi^{4, 10, 11,12},Galapagos^{4,8,10,11}, Janssen^{4,10,11}, Lilly^{4,5,7,10,11,12}, Medac^{4,10},MSD^{4, 11}, NORDIC Pharma^{4, 10, 11, 12}, Novartis^{4, 5, 8, 10, 11}, OWKIN^{4,10}, Pfizer^{4, 5, 8, 10, 11,12}, Roche^{4, 10}, Sanofi-Genzyme^{4, 5, 10, 12}, SOBI^{4,8, 10,11}, UCB^{4, 8, 10, 11}, Viatrix^{4, 11}.

JK: Galapagos^{10,14}, Chugai¹⁰, BMS¹¹, UCB^{11,14}, Amgen¹⁴.

PAJ declares that he has no competing interest.

CR: BMS¹¹, AbbVie¹¹, UCB¹¹.

JD declares that she has no competing interest.

JA: Lilly^{10, 11}, Galapagos^{5, 7, 9, 10, 11}, Pfizer¹¹, Abbvie^{7, 10,11}, Bristol Myers Squibb^{5, 10, 11}, Sanofi^{10, 11}, Nordic^{5, 10, 11},Medac¹¹, Fresenius kabi^{5, 10, 11}, Novartis¹¹, Biogen¹¹, Sandoz¹¹,AstraZeneca¹¹, Boehringer¹¹, MSD¹¹.

AB: Janssen^{8, 12}, Fresenius^{8, 11}, Abbvie⁸, BMS¹², Sandoz⁵Galapagos^{10,11}, Novartis^{10,11}, Nordic¹¹, Chugai⁵.

OB: AbbVie^{7,11}, BMS^{7,11}, MSD¹¹, Nordic¹¹, Pfizer^{7,11}, Roche-Chugai¹¹, UCB^{7,11}, Novartis^{7,11}, Janssen¹¹, Lilly^{7,11}.

GCA: Abbvie^{8,11}, Biogen¹⁰, BMS^{8,10,11}, Chugai¹¹, Galapagos^{10,11}, Lilly^{10,11}, MSD¹⁰, Novartis⁸, Pfizer^{10,11}.

AC: Abbvie7,10,11, Amgen11, Biogen11, BMS7,10,11,Boehringer10,11, Celltrion7,10,11, Fresenius Kabi10,11, Galapagos7,10,11, Janssen7,10,11, Lilly7,10,11, Medac11, MSD11, Novartis7,10,11, Pfizer7,10,11, Roche Chugai7,10,11, Sanofi11, Sandoz11, UCB10,11, Viatris11.

ED: Abbvie11,Amgen SAS11, ASTRAZENECA11, BMS10,11,Galapagos8,11, GSK11, Janssen-Cilag10,11, Lilly France5,10,11,MSD10,11, NORDIC-Pharma7,8,11,Novartis5,7,8,10,11, Pfizer11,Roche-ChugaiI8,10,11, UCB10,11.

CGV declares that she has no competing interest.

VG: AbbVie11, MSD11, Lilly10,11, Galapagos11, GSK11, Medac10,11,Fresenius Kabi14.

JEG declares that he has no competing interest.

BLG: Abbvie8,1011, MSD11, BMS8,10, Pfizer11, Novartis6,10,8,11,Roche-Chugai6,8,11, AMGEN11, Fresenius-Kabi11, Viatris11, Lilly11,Sandoz6,11.

HM: Abbvie8,11, Accord5, Biogen5,11, Bristol Myers Squibb,11,Celltrion HealthCare2,4,5,6,11, Fresenius Kabi5, Galapagos5,8,11,GSK5,11, Janssen4, Lilly France4,6,11, Medac6,11, Merck Sharp &Dohme11, Novartis4,8,11, Nordic Pharma4,5, Pfizer11, and SanofiAventis7,11.

CR: Lilly10, Celltrion10, Pfizer10, AbbVie10, Novartis10, Biogen10,Medac10, Astra Zeneca10, GSK10, MSD10, Amgen10, Ono10, Mylan10,Glenmark10, BMS10, Roche10, Chugai10, UCB10, Fresenius Kabi10,Galapagos10, Sandoz10, Janssen-Cilag10, Sanofi-Aventis10.

JHS: Abbvie4,11, BMS4,11, Galapagos4,8,11, Lilly4,8,11, Janssen4,MSD11, Novartis8,11, Pfizer4,11, Roche11, Sanofi11and UCB4,11.

AS: Abbvie11, Bristol Myers Squibb11, Janssen11, Lilly France7,11, Merck Sharp11, MSD11, Nordic11, Novartis8, 11, Pfizer11, RocheChugai7, UCB11.

ES: Fresenius Kabi11, celltrion7 11, Lilly4, Nordic4,7,10, Sandoz4,11,AbbVie4,11, Pfizer11, IQVIA11, Medac11, UCB11, Ipsen12.

RS: Sanofi10, GSK7,10,11, UCB10, Roche10, BMS7,10,100,Nordic10, Pfizer10, Celgene10, Amgen10, Lilly10, Fresenius Kabi10,Boehringer10,11, Janssen10, Novartis7,10, Biogen10, Kiniksa10,Servier7, Astra Zeneca11.

AT: Abbvie8, 10, 11, Sanofi Aventis10,11, MSD Chibret11,Novartis6,10, Lilly France8,10,11, Roche5,11, Pfizer6,11, Fresenius Kabi5,8, 10,11, Sandoz8, Biogen8, UCB6,10, Celltrion5,8, 11, Janssen8,11,Medac11.

OV: BMS7,10,11, Pfizer11, Lilly7,11, Novartis10,11, Biogen10,11,Sandoz7, AbbVie10,11, MSD11, Mylan7,11, Galapagos10,11, Chugai7,Amgen7, Janssen11, UCB10,11.

PE: Abbvie12, BMS12, Roche-Chugai12, Pfizer12, MSD12, UCBPharma12, Lilly12, Sanofi12, Sandoz12, Boehringer Ingelheim12, Galapagos12, Janssen12, Fondation Apicil12.

DV declares that he has no competing interest.

PD: Boehringer Ingelheim2,4,8,9,10,11, Pfizer4,5,6,9,11, Bristol-Myers Squibb4,5,6,7,9,10,11, Galapagos5,11,12, Lilly9,11, Abbvie10, 11, Chugai10,11, Janssen10,11.

CD: Amgen4,7,10,11, Servier2,4,9,10,11,12, Procter & Gamble8,11,12, Sanofi-Aventis8,11,12, MSD4,10,11,12, Novartis4,5,8,10,11,12, LillyFrance4,8,10,11, Roche4,10,11, GSK4,10,11, Nycomed4,10,11.16

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