



## Review

## Systemic rheumatic diseases: From biological agents to small molecules

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## ABSTRACT

The development of biologics and small oral molecules has recently changed the scenario of pharmacologic treatment of systemic rheumatic diseases and it has become a real revolution. These drugs have innovative mechanisms of action, based on the inhibition of specific molecular or cellular targets directly involved in disease pathogenesis.

This new scenario has led to a regular update of the management recommendations of several institutions, such as those for Rheumatoid Arthritis treatment that address the use of conventional and biologic therapies including TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), abatacept, rituximab, IL-6 inhibitors (tocilizumab and sarilumab), biosimilars and small oral molecules (the JAK inhibitors tofacitinib and baricitinib). Monotherapy, combination therapy, treatment strategies (such as treat-to-target) and the targets of sustained clinical remission or low disease activity are the final goal of the guidelines for rheumatic patients management. In another condition represented by Axial Spondyloarthritis guidelines suggest to start first with non-steroidal anti-inflammatory drugs to improve lifestyle and reduce spine inflammation, but if this is not achieved in 2–4 weeks it is important to consider the use of local therapies (i.e. glucocorticoid injections) or to start biologic therapy such as TNF inhibitors and then eventually switching to another TNF inhibitor or swapping to IL-17 inhibitor. In the case of active Psoriatic Arthritis, guidelines suggest to start with non-steroidal anti-inflammatory drugs and even local glucocorticoid injections especially for oligoarthritis, then to start conventional therapies if lack of efficacy, and finally start biologics or small oral molecules in the presence of drugs toxicity, unfavorable prognostic factors and still active arthritis. In several cases, active Psoriatic Arthritis patients develop a complex clinical condition with comorbidities such as diabetes, inflammatory bowel disease and high risk of infections, and for this reason the American College of Rheumatology and the National Psoriasis Foundation have developed specific guidelines for their management.

Biologic and new small molecules therapies are very expensive, but the availability of biosimilars offers the opportunity of reducing the treatment cost and significantly decreasing the cost of originators as well. In fact, we live in a period characterized by the need to rationalize costs of these drugs, to allow treating a higher number of patients and to maintain a homogeneous possibility of treatment choice. For these reasons, we need to follow scientific guidelines and patients' clinical conditions to choose the correct treatment, also based on the economic burden of therapies.

**Abbreviations:** ANCAs, anti-neutrophil cytoplasmic antibodies; AxSpa, ankylosing spondylitis; BD, Behçet's disease; bDMARDs, biological DMARDs; CCP, cyclic citrullinated peptides; CD, Crohn's disease; cDMARDs, conventional DMARDs; CRP, C-reactive protein; DMARDs, disease-modifying anti-rheumatic drugs; EMA, European Medicines Agency; ESR, erythrocyte sedimentation rate; EULAR, European League against Rheumatism; FDA, Food and Drug Administration; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; JAK, Janus kinase; JAKin, JAK inhibitors; IBD, inflammatory bowel disease; i.v., intravenous; LFN, leflunomide; mAb, monoclonal antibody; MTX, methotrexate; MTX-IR, incomplete responder to MTX; NPF, National Psoriasis Foundation; NSAIDs, non-steroidal anti-inflammatory drugs; OSM, oral small molecules; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; RCT, randomised controlled trial; ReA, reactive arthritis; RF, rheumatoid factor; s.c., subcutaneous; tsDMARDs, targeted synthetic DMARDs; SSZ, sulfasalazine; TNF $\alpha$ , tumour necrosis factor alpha; TNFin, TNF inhibitor; UC, ulcerative colitis; TRAPS, TNF receptor-associated periodic syndrome

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## 1. Introduction

The development of biological agents and, more recently, oral small molecules whose innovative mechanisms of action are based on inhibiting specific molecular or cellular targets directly involved in disease pathogenesis has revolutionised the pharmacological treatment of systemic rheumatic diseases. The results of randomised clinical trials (RCTs) and real-life reports from national registries have clarified many of the aspects of biological disease-modifying anti-rheumatic drugs (bDMARDs) in patients with inflammatory rheumatic disorders, including their mechanisms of action, efficacy and safety, and the possibility of optimising their use in individual patients in order to ensure personalised medicine. However, the data concerning Janus kinase (JAK) inhibitors only come from RCTs, and we still need to discover from registries and real-life experience what their role in future treatment strategies will be.

The therapeutic models considered in this review are rheumatoid arthritis (RA), ankylosing spondyloarthritis (AxSpA), and psoriatic arthritis (PsA).

### 1.1. Biological therapies

#### 1.1.1. Biological anti-TNF $\alpha$ agents for the treatment of RA

Tumour necrosis factor alpha (TNF $\alpha$ ) is an important host defence molecule involved in the acute phase reaction induced by inflammation and capable of recruiting other pro-inflammatory mediators after its release [1]. It is the target of five specific inhibitors (TNFin) that have been approved since 2000 (Fig. 1): intravenously administered (i.v.) infliximab, and subcutaneously administered (s.c.) adalimumab, certolizumab pegol, etanercept and golimumab [2,3]. All these molecules are monoclonal antibodies (mAbs) or fragments of mAbs, while etanercept is a fusion protein composed of the 2 extracellular portions of the human TNF receptor 2 (p75 TNF receptor) and the Fc portion (hinge, CH2 and CH3 domains) of human IgG1 (Fig. 1) [4]. Anti-TNF $\alpha$  agents have proved to be safe when correctly prescribed and monitored [5–7] and, over the last 20 years, have been approved for the treatment of various inflammatory diseases: RA, juvenile idiopathic arthritis, PsA, AxSpA, psoriasis (PsO), Crohn's disease (CD), ulcerative colitis (UC), and Behçet's disease (BD) [8,9]. However, although all of these anti-TNF $\alpha$  agents are very effective in RA, PsA and AxSpA, they are not equally efficacious in CD and UC as infliximab, adalimumab and

golimumab can induce the clinical and endoscopic remission of inflammatory bowel disease (IBD), which is not true for the soluble etanercept [10].

It has been demonstrated that TNFin are effective and well tolerated in a large proportion of patients involved in RCTs, but primary and secondary failures of TNFin strategies affect 30–50% of patients treated in clinical practice, particularly those with long-standing diseases [11]. For this reason, a number of other bDMARDs has been developed and approved for treatment in the case of the failure of anti-TNF $\alpha$  therapy (Fig. 1), and they will be discussed in the next paragraphs.

#### 1.1.2. Non-anti-TNF $\alpha$ biological agents for the treatment of RA

In more recent years, additional biologics with different targets and mechanisms of action have been developed for the treatment of rheumatic diseases (Fig. 1).

Abatacept, a recombinant fusion protein that selectively modulates a co-stimulatory signal necessary for T-cell activation, is currently approved in the EU for use in patients with highly active and progressive RA who have not previously received methotrexate (MTX) or who have inadequately responded to previous treatment with at least one conventional DMARD (cDMARD) including MTX, or TNFin [12,13]. In phase III trials, beneficial effects on RA signs and symptoms, disease activity, structural damage progression and physical function were seen with both i.v. or s.c. abatacept regimens, in particular in association with methotrexate [14]. Abatacept was also authorised for the treatment of active PsA [15] in the USA (July 2017) and by the EMA (August 2017) (Figs. 1 and 2).

Tocilizumab is an IL-6 receptor antagonist that is approved (with and without MTX) for the treatment of adults with moderate to severe active RA. Extensive clinical experience with both i.v. and s.c. regimens has firmly established their short- and long-term efficacy and safety in adults with early-stage or established RA [16]. In clinical trials and the real world settings, tocilizumab leads to a rapid and sustained improvement in clinical and radiographic outcomes and the health-related quality of life [17]. The safety profile of tocilizumab is comparable to other immunomodulatory agents, with low risk of immunogenicity, and it is now available both in i.v. and s.c. administration to treat severe, active and progressive RA in adults. Tocilizumab is indicated in RA patients with or without previous methotrexate treatments, as first or second-line biologic therapy, in case of adult RA patients who responded inadequately or were intolerant to previous therapy with at

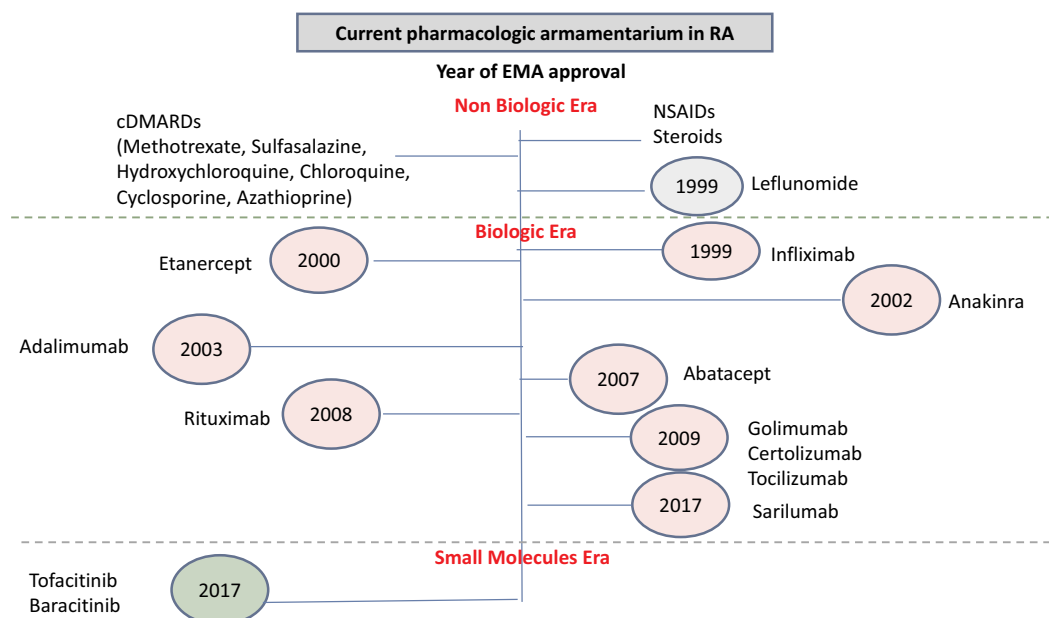


Fig. 1. Current RA pharmacological armamentarium. The name of each drug is given with the year of EMA approval.

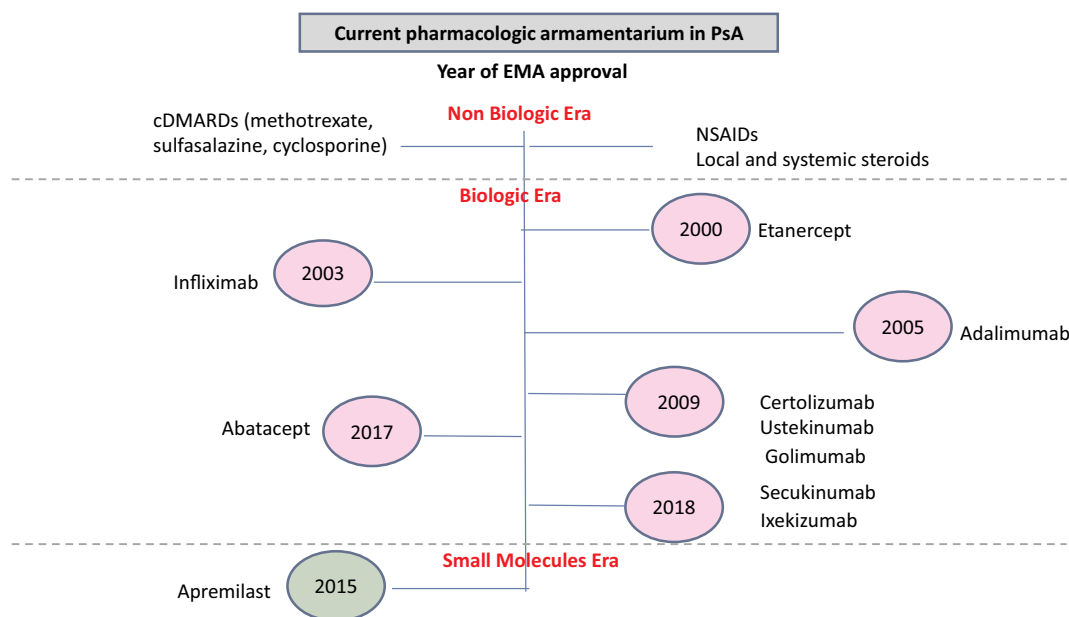


Fig. 2. Current PsA pharmacological armamentarium. The name of each drug is given with the year of EMA approval.

least one cDMARD or TNFin [18].

Rituximab, which was originally used to treat non-Hodgkin's lymphoma, was later approved for the treatment of RA and anti-neutrophil cytoplasmic antibody(ANCA)-associated vasculitis. It is a mAb against the CD20 molecules expressed on the surface of pre-B and mature B lymphocytes, whose apoptosis is caused as a result of its antibody- and complement-dependent cytotoxicity. Rituximab is currently used in rheumatology not only to treat RA [19], but also in the off-label treatment of severe organ involvement in patients with Systemic Sclerosis, Sjögren's Syndrome and Systemic Lupus Erythematosus [20].

Sarilumab is a recently developed anti-IL-6 drug that specifically targets soluble and membrane-bound IL-6 receptors. It is administered subcutaneously every two weeks, and significantly improves disease activity in patients responding inadequately to methotrexate and TNFin. It has proved to be superior to adalimumab monotherapy in improving clinical disease activity in RA patients unable to continue MTX (ACR 20 response rates of 71.1% vs 58.4%) [21].

Anakinra is an IL1 receptor antagonist that was initially approved for the treatment of RA in 2002, but it is currently approved for the treatment of arthritis, specific conditions such as Schnitzler's syndrome and auto-inflammatory diseases for which first-line treatments are not effective [22], and also for familial Mediterranean fever, hyper-IgD syndrome, and TNF receptor-associated periodic syndrome (TRAPS) [23].

1.1.3. Non-anti-TNFα biological agents for the treatment of AxSpA and PsA

Over the last few years, a variety of non-anti-TNFα drugs have been approved for the treatment of AxSpA and PsA by the US Federal Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Two biological drugs of proven efficacy are ustekinumab (approved by the EMA in 2009 and by the FDA in 2013) and secukinumab (approved by the EMA in 2015 and by the FDA in 2016) [24,25](Fig. 2 and Table 1).

Ustekinumab is a biologic therapy that binds specifically to the p40 subunit of IL12 and IL23, thus inhibiting downstream the Th17 signalling pathways. Its efficacy has been proven in two phase III clinical trials in PsA [26], which demonstrated: i) no particular safety signals; ii) consistent clinical efficacy, similarly to what reported in PsO [27], and also in trials for treatment of moderate-to-severe CD [28], without raising any safety issues. It is currently approved for the treatment of PsA following the failure of NSAIDs and cDMARDs, and as an

Table 1

Biological agents and small molecules approved for the treatment of PsA.

Drug	Mechanism of action	Year of FDA approval	Year of EMA approval
Ixekizumab	IL-17 inhibition	2017	2018
Tofacitinib	JAK1 inhibition	2017	2018
Abatacept	Inhibition of CD28-CD80/86 interactions	2017	2017
Golimumab	Anti-TNF	2017	2009
Secukinumab	IL-17 inhibition	2016	2015
Apremilast	PDE4 inhibition	2014	2015
Certolizumab	Anti-TNF	2013	2013
Ustekinumab	IL12/23 inhibition	2009	2014
Adalimumab	Anti-TNF	2005	2005
Infliximab	Anti TNF	2005	2003
Etanercept	Anti-TNF	2002	2000

alternative to or after the failure of anti-TNFα agents [26].

Secukinumab, which has recently been approved for the treatment of skin PsO, PsA and AxSpA, is a human immunoglobulin(Ig)-G1-κ mAb that binds to the IL17A receptor and thus interrupts its inflammatory cascade [29] (Table 1). In addition to its efficacy in treating arthritis, it has proved to be efficacious in treating dactylitis, enthesitis, and skin and nail PsO. Moreover, its safety profile and satisfactory medium- and long-term outcome data suggest that it could have a significant impact on treatment algorithms [30], as will be discussed below.

Ixekizumab is a humanised mAb that blocks IL17 and has been very successfully used to treat adult moderate-severe plaque PsO. It was approved for the treatment of active PsA by the FDA in December 2017, and by the EMA in 2018 [31] (Table 1).

1.2. Non-biological therapies

1.2.1. JAK inhibitors for the treatment of RA

Cytokines are key drivers of inflammation in RA patients and, over the last 20 years, anti-cytokine therapies have significantly improved disease outcomes. Now, a new field of cytokine research has been investigating the blockade of Janus kinases (JAK), a family of intra-cellular and non-receptor tyrosine kinases linked to the intra-cellular domain of many cytokine receptors [32]. There are four JAK isoforms (JAK1, JAK2, JAK3 and TYK2), and various cytokine receptor families

**Table 2**  
Biological agents and small molecules under development for inflammatory rheumatic diseases.

Drug	Disease	Mechanism of action	Trial phase	Name of trial
Filgotinib	PsA	JAK1 inhibition	Phase 2	Equator
	RA		Phase 3	Finch 2
	SpA		Phase 2	Tortuga
Upadacitinib	RA	JAK1 inhibition	Phase 3	Select-next
	SpA		Phase 2	Select Axis 1
Guselkumab	PsA	IL23p19 inhibition	Phase 2	NCT 02319759
Bimekizumab	PsA	IL17 A-F inhibition	Phase 3	<a href="#">NCT02963506</a> <a href="#">NCT03355573</a>
	SpA		Phase 2	<a href="#">NCT02430909</a>
	RA		Phase 2	
BCD-085	PsA	IL 17 inhibition	Phase 3	PATERA
Brodalumab (siliq)	PsA	IL 17 inhibition	Phase 3	
Clazakizumab	PsA	IL 6 inhibition	Phase 2	
AMG 592	RA	LT regulation	Phase 2	
Sarilumab	PsA	IL6 inhibition	Phase 2	
Mavrilimumab	RA	GM-CSF pathway inhibition	Phase 2	
GSK3196165	RA	Anti-GM-CSF	Phase 2	
Namilumab	RA	Anti-GM-CSF	Phase 2	
MORAb-022	RA	Anti-GM-CSF	Phase 1	
DEN-181 1	RA	LT regulation	Phase 1	
Dercernotinib	RA	JAK3 inhibition	Phase 2/3	
Peficitinib	RA	JAK 1–3 inhibition	Phase 3	RAJ3-RAJ4

use specific JAK isoforms for intracellular signal transduction. JAK phosphorylates cytokine-bound receptors, and this triggers the intracellular molecules that eventually lead to gene transcription [33]. Two oral JAK inhibitors (JAKin) [34,35] called tofacitinib and baricitinib have recently been approved for the treatment of RA, and many others are currently under development (Table 2).

Tofacitinib is a potent, selective inhibitor of JAK1 and JAK3 that has been approved in the EU for the treatment of moderate-severe active RA at an oral dose of 5 mg twice daily in adults who are unresponsive or intolerant to cDMARDs [36]. Clinical studies of less than 2-year duration have shown that tofacitinib alone (as first or second line treatment) or combined with a cDMARD is effective in reducing RA signs and symptoms, with improvement of health-related quality of life during long-term therapy [37]. As for the safety profile, tofacitinib is generally well tolerated, with most adverse events of mild or moderate severity similar to those related to biological drugs, particularly infections [38]. A specific alert has been issued on the risk of herpes zoster infection in tofacitinib-treated patients, even though it was represented by clinically mild forms of infection [39].

Baricitinib is an oral, selective, and reversible inhibitor of JAK1 and JAK2 [40] that demonstrated a significant improvement in histologic and radiographic signs of RA in pre-clinical animal models of arthritis, with no evidence of suppressed humoral immunity or adverse hematological effects [41]. Thanks to the positive results also obtained in phase II and III clinical trials [42], baricitinib was approved in the EU and in Japan for the treatment of moderate to severe RA in patients with inadequate response to cDMARDs, at two different dosages (2 and 4 mg daily), as monotherapy or in combination with methotrexate [43]. The EMA Committee for Medicinal Products for Human Use recently updated the baricitinib label with a warning for patients at risk of developing thrombo-embolic diseases [44–46].

### 1.2.2. Small molecules for the treatment of PsA

A new therapy for PsA patients called apremilast, an orally administered small molecule that inhibits the phosphodiesterase 4 (PDE4) [47,48] has been approved in 2014 by the FDA and in 2015 by the EMA (Table 1). Its approval has been obtained for a dosage of 30 mg twice daily after demonstrating its capacity to reduce the severity of moderate to severe plaque PsO in the phase 3 ESTEEM trials [49], and improved difficult-to-treat nail, scalp and palmoplantar PsO. Most patients reported significantly improved outcomes in comparison to placebo after only two weeks of treatment. The phase III PALACE trials [50] showed

that it improved the signs and symptoms of PsA (enthesitis, dactylitis, physical function and fatigue) in both cDMARD-naïve and cDMARD-experienced patients with active PsA, and this effect was maintained for up to 208 weeks. The phase IIIb ACTIVE trial [51] showed that it has an early onset of action in patients with active PsA, who achieved ACR20 responses after two weeks of treatment. In terms of safety, apremilast does not require any specific laboratory monitoring and is well tolerated except for the onset of gastrointestinal side effects (diarrhea, nausea), which improve after the first few days of treatment [52].

### 1.3. Biosimilars

In the last few years, the use of drugs called “biosimilars” has become larger and larger in rheumatology, due to the patent expiration of traditional biologic therapies. With the term biosimilars we refer to highly similar copies of originator biologics approved through pre-defined and stringent regulatory processes after rigorous physicochemical, non-clinical, and clinical evaluations [53]. The EULAR states that efficacy and safety of biosimilars approved by the EMA or FDA are similar to those of the biological originator, and that they should be preferred if they are appreciably less expensive than the originator or other biological compounds [54]. Biosimilars of the anti-TNF $\alpha$  agents infliximab, adalimumab and etanercept are already widely available [55], and more recently also the biosimilar of rituximab has been approved for use in RA patients, and several additional biosimilars are in the pipeline for future use [56].

The introduction of TNFin revolutionised RA treatment in the early 2000s, but associated financial burden is significant: for example, the estimated annual per-patient cost of Enbrel (etanercept) is £9295 in the United Kingdom (UK) and \$15,345 in the USA [57]. For this reason, there is great interest in developing biosimilars that cost significantly less than their originators [58]. However, although reduced costs and greater patient access to biosimilars are changing therapeutic choices in clinical practice, it is essential to develop and maintain specific and rigorous regulatory guidelines for their development and approval throughout the world.

### 1.4. Treatment guidelines

#### 1.4.1. Rheumatoid arthritis (RA)

RA is a chronic, autoimmune, systemic inflammatory disorder that symmetrically affects small and large synovial joints, and significantly

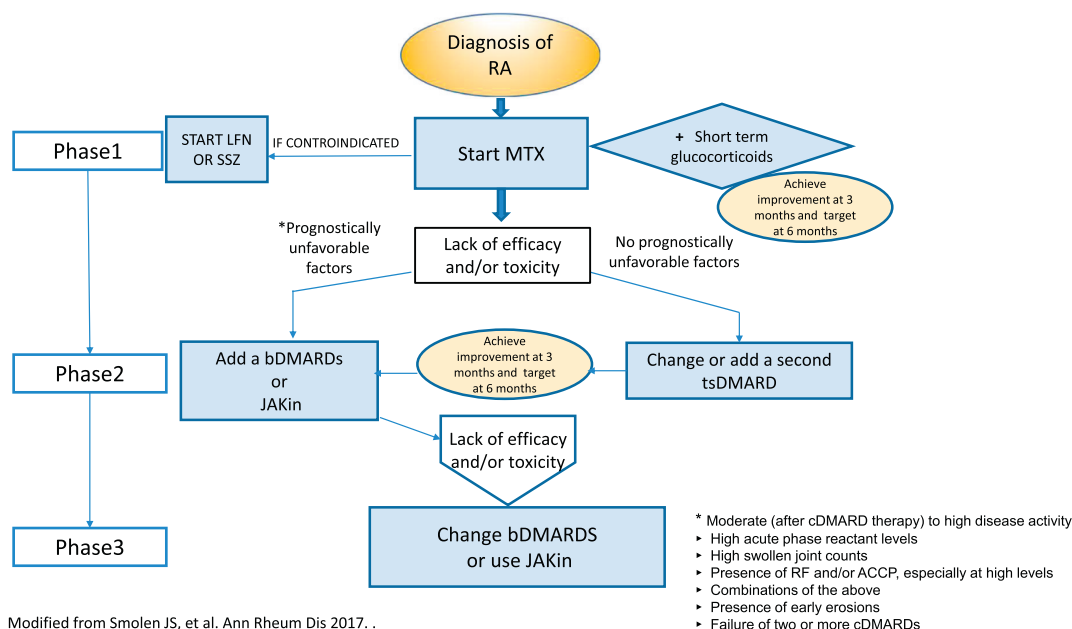


Fig. 3. Schematic illustration of the 2016 EULAR recommendations for the management of RA (modified from Smolen JS, et al. Ann Rheum Dis 2017;76:960–977; [60]).

reduces patients' quality of life and life expectancy if left untreated. The development of a pannus is pathologically central to the mechanism of joint destruction, but its molecular basis and the pathways by which synovial fibroblasts achieve and maintain an aggressive phenotype are still unknown. There is no cure for RA, but patients can be treated with long-term cDMARDs in order to suppress joint inflammation, minimise joint damage, preserve joint function, and maintain disease remission [59]. According to the recently updated EULAR recommendations [60], cDMARD treatment should be started immediately after the diagnosis of RA, and MTX should be part of the first treatment strategy (Fig. 3). Unfortunately, MTX does not induce remission or minimal disease activity in a large proportion of patients: in these cases [60], and in patients with negative prognostic factors (such as rheumatoid factor, anti-CCP antibodies, early erosions, high levels of acute-phase reactants), bDMARDs or tsDMARDs should be considered [61].

In patients considered MTX-IR (MTX incomplete responders), neither the EULAR nor the ACR recommendations indicate the use of one specific bDMARD or tsDMARD [62–64]. The similar efficacy within all bDMARDs when used in combination with MTX is generally reported, even though about 30% of patients in clinical practice need to be treated with bDMARDs in monotherapy because intolerant to MTX [65].

There is still ambiguity on the strategy to apply in the treatment of RA patients who have an inadequate response to the first TNFIn, but observational data confirm the advantage in changing the mode of action in TNF-IR, what is called “swap” method [63]. ACR recommendations suggest to use a non-TNF biological drug in case of insufficient response to the first TNFIn, while EULAR recommends to use a second TNFIn or a drug with a different mode of action [60]. Patients with secondary inefficacy to TNFIn may have lost response because of the development of antidrug antibodies, and these patients would be expected to exhibit a clinically relevant response to an antigenically distinct treatment [66,67].

Changing the mode of action is also worth considering because abatacept, golimumab, rituximab, tocilizumab, tofacitinib and baricitinib have all proved to be clinically efficacious in patients with a previously inadequate response to at least one TNFIn [68,69].

If a patient is in persistent remission after tapering steroids, tapering bDMARDs can be considered, but the abrupt discontinuation of bDMARD treatment leads to flares in most patients, and not all of these

regain their former remission or low disease activity status after resuming bDMARDs [70,71].

#### 1.4.2. Spondyloarthropathies (SpA)

SpA are a family of chronic rheumatic conditions characterized by spine and joint inflammation. They may have different names depending on their main disease manifestations (AxSpA, PsA, reactive arthritis [ReA], and arthropathy related to IBD), but their collective prevalence is similar to that of RA [72]. In addition to the two main forms of “axial” and “peripheral” SpA (respectively based on spine and joint involvement), SpA may also be associated with enthesitis, dactylitis and extra-articular manifestations such as IBD [73,74]. The disease burden can lead to significant disability, especially in the case of a delayed diagnosis, which is often due to the fact that there is no specific diagnostic biomarker, and the strong genetic component and familial heritability of SpA is still unclear. Although HLA-B27 is closely associated with the severity and persistence of axial SpAs, there is ample evidence suggesting that they are highly heterogeneous and polygenic disorders [75].

NSAIDs have long been used in the first-line treatment of SpA, with TNFIn being considered in the case of persistent disease activity or an insufficient response to standard treatment [76]. Despite their efficacy, a significant proportion of SpA patients do not reach clinical remission with TNFIn, thus it is necessary to use different mechanisms of action [77], and for this purpose additional biological agents have been approved and they are under evaluation [78]. Once AxSpA has been correctly diagnosed, it is necessary to start NSAIDs and improve lifestyles in order to reduce spine inflammation. If this is not achieved within 2–4 weeks, it is important to consider the use of local therapies (i.e. glucocorticoid injections) or start bDMARD treatment with a TNF $\alpha$  blocker and, if necessary, switching to another TNFIn or swapping to an IL17in [78] (Fig. 4).

#### 1.4.3. Psoriatic arthritis (PsA)

PsA is a chronic, inflammatory, musculoskeletal disease associated with PsO (30% of cases), and frequently leads to the development of peripheral arthritis, dactylitis, enthesitis, and spondylitis. Nail lesions, including pitting and onycholysis, occur in ~80–90% of PsA patients, and may even be the only expression of PsO. The distribution of peripheral arthritis varies from asymmetric oligoarthritis (involving  $\leq 4$



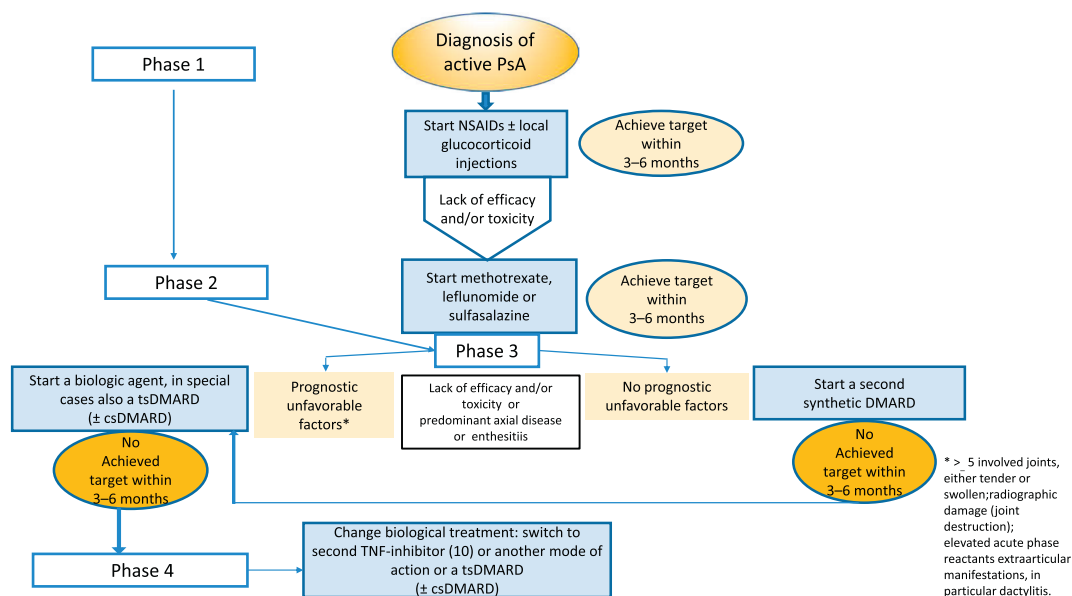


Fig. 5. Schematic illustration of the 2016 EULAR recommendations for the management of active PsA (modified from Gossec L, et al. Ann Rheum Dis. 2016;75:499–510).

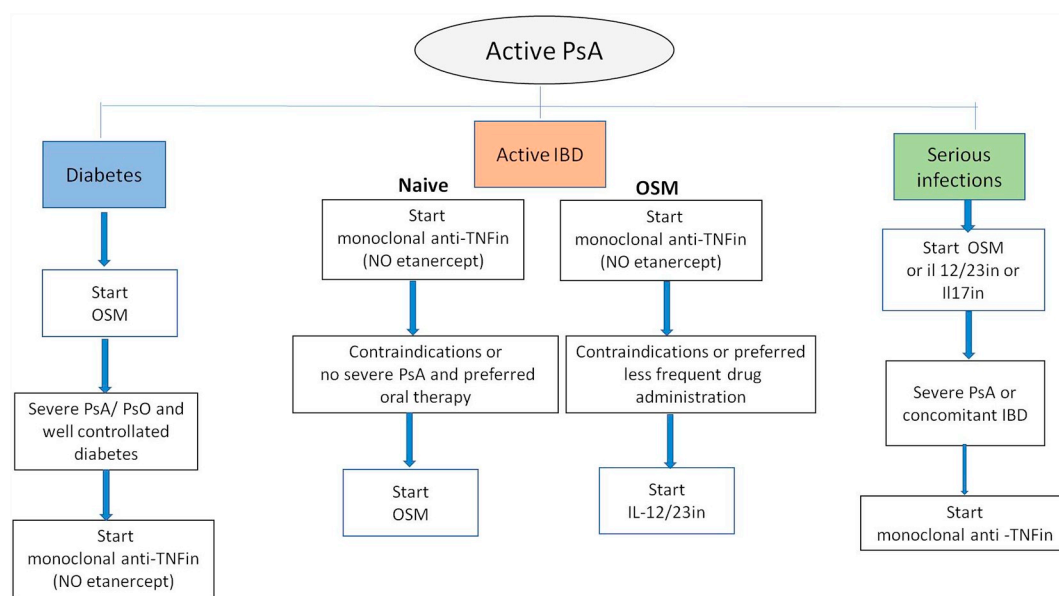


Fig. 6. Schematic illustration of the 2018 ACR/National Psoriasis Foundation Guidelines for the Treatment of Psoriatic Arthritis with co-morbidities (modified from Singh JA, et al. Arthritis Care & Research 2019; 2: 2–29; [83]).

recommendations for the management of PsA in 2016 [78] (Fig. 5) because the new treatments, assessments and evidence concerning co-morbidities in PsA patients [83] requires a substantial revision of treatment strategies (Fig. 6). In particular, the 2018 ACR/NPF PsA guidelines [83] (Fig. 6) can also be used by health care providers and patients to select the appropriate therapy in common clinical scenarios as treatment decisions should consider the situation of each individual patient, and guidelines should be used taking co-morbidities into account.

1.4.5. Personalised (precision) medicine in rheumatology: is it influenced by treatment costs in the era of biosimilars?

One of the unmet needs in rheumatology is the lack of reliable biomarkers for diagnosing rheumatic diseases such as PsA [90] and its subtypes, and choosing the specific treatment for individual patients [91]. For this reason, it is necessary to follow general rules, protocols

and guidelines when prescribing [92,93], and often necessary to try several treatments before finding the most appropriate one for each patient. As inflammation biomarkers such as ESR and CRP only provide general information concerning disease activity and, alone, are not sufficiently predictive to be used for treatment decision making, researchers are still trying to identify better ways of monitoring patients during specific treatments [94].

The detection of autoantibodies such as RF and anti-CCP antibodies is included in the EULAR/ ACR diagnostic criteria for RA [95], and can guide the choice of treatments aimed at preventing or slowing the development of symptomatic RA. Unfortunately, no biomarker has been identified to detect the 30% of PsO patients who will develop PsA, its clinical phenotype (i.e. axial or peripheral), or to decide on the best targeted biological agent.

The prospect of being able to use biomarkers to ensure the personalised treatment of rheumatic conditions has not yet led to any

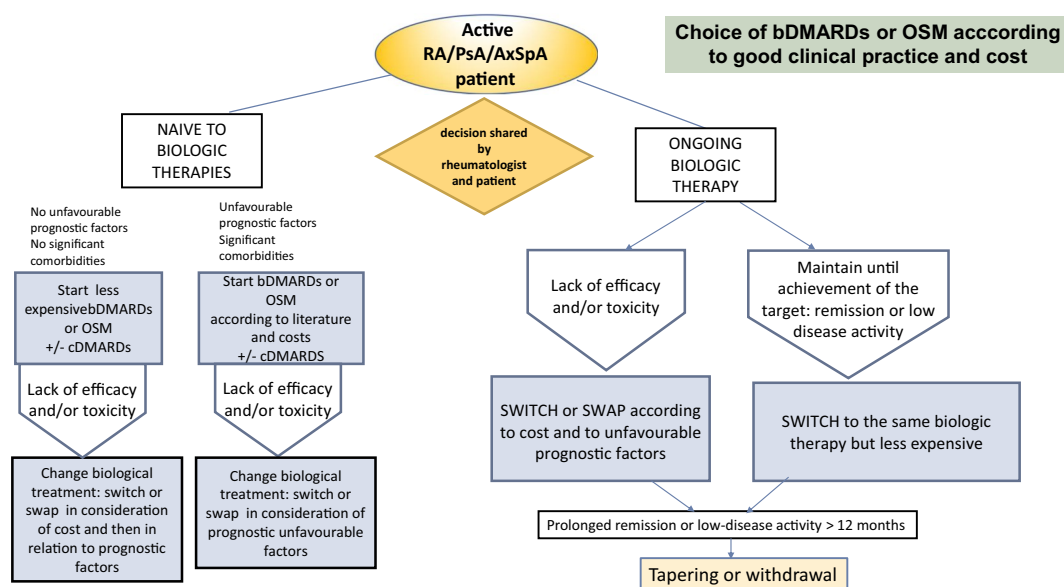


Fig. 7. A possible algorithm for choosing bDMARDs or oral small molecules on the basis of good clinical practice and cost.

significant clinical applications, and some authors are pessimistic as to whether it ever will. However, researchers are still very active in this field; for example, the multibiomarker disease activity panel (MBDA) marketed in the United States under the name VectraDA has been approved by the FDA as a means of assessing RA disease activity [96]. It is based on simultaneous measuring 12 proteins in blood, and then converting to the results into a single numerical value using a proprietary calculation, but its use is still a matter of debate.

The recent development of biological drugs (originators and biosimilars) has profoundly changed the management of patients affected by chronic inflammatory rheumatic diseases who do not respond to cDMARDs. Unfortunately, biological treatments are very expensive [54,97] and we live at a time when it is necessary to rationalize costs in order to allow a larger number of patients to be treated and maintain equal access to preferred treatments; for these reasons, although the choice of the most appropriate treatment should be based on the scientific guidelines and the patient's clinical condition, consideration should also be given to the economic burden of the treatments themselves [98].

It is fundamental to involve patients in the choice of treatment when the disease remains active despite cDMARDs [99]. One of the most debated and controversial aspects of modern rheumatology is that switching treatments may be automatically and solely based on economic grounds, without making a correct cost/efficacy evaluation or giving sufficient consideration to patients' needs or preferences, their clinical features, or whether they are bDMARD naïve or experienced. We still do not have clear guidelines concerning the efficacy and safety of the multiple switching of biosimilars of the same originator, which is why it is important to create specific registries to monitor switching strategies. This is a complex and ever-changing subject but scientific societies have started developing position papers on how to use biosimilars [98], and these agree that the least expensive bDMARD should be used in treatment-naïve patients, and that the choice of a bDMARD in treatment-experienced patients should be based on their real-life clinical condition.

Fig. 7 shows a possible algorithm for choosing bDMARDs or small oral molecules on the basis of good clinical practice and cost. However, in addition to these aspects, we also need to consider treatment responses, the responses achieved after switching therapies, reducing or discontinuing treatment in the case of remission, therapy adherence, and appropriate medical follow-up.

## 2. Conclusions and future plans

An early diagnosis and personalised treatment are considered fundamental in preventing or minimising joint and bone damage in patients with rheumatic diseases such as RA and SpA. The early identification of inflammatory rheumatic diseases is crucial, and its importance should be stressed to general practitioners and the population as a whole. It is also important to start treatment as soon as possible after even a rapid rheumatological evaluation raises the suspicion of RA or SpA. The recent establishment of “early arthritis clinics” ensures that early-onset arthritis can be promptly treated despite the potential risk of over-treating a form of arthritis that may not evolve into full-blown rheumatic disease. Starting treatment within three months of disease onset is the most important means of achieving remission, but can be difficult because of the lack of specific measures of disease activity, disease remission or low disease activity. Frequent follow-up visits are particularly important in order to respect the over-arching principle of treating-to-target and ensure successful treatment, improve prognosis, and offer patients a better quality of life.

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