Autoimmunity Reviews 18 (2019) 583–592

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Systemic rheumatic diseases: From biological agents to small molecules

Piercarlo Sarzi-Puttini[a,*], Angela Ceribelli[a], Daniela Marotto[b], Alberto Batticciotto[c], Fabiola Atzeni[d]

[a] Rheumatology Unit, ASST Fatebenefratelli-Sacco, University of Milan, Italy
[b] Rheumatology Unit, P-Dettori Hospital, Tempio Pausania, Italy
[c] Rheumatology Unit, Internal Medicine Department, ASST Settelaghi, Ospedale Di Circolo - Fondazione Macchi, Varese, Italy
[d] Rheumatology Unit, University of Messina, Messina, Italy

ARTICLE INFO

Keywords:
Biological therapies
Biosimilars
Rheumatoid arthritis
Spondyloartropathies
Psoriatic arthritis
Small molecules
Guidelines
Recommendations

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 lead 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; TNFα, tumour necrosis factor alpha; TNFin, TNF inhibitor; UC, ulcerative colitis; TRAPS, TNF receptor-associated periodic syndrome

* Corresponding author at: Rheumatology Unit, ASST Fatebenefratelli-Sacco, University of Milan, Via GB Grassi 74, 20157 Milano, Italy.
E-mail address: piercarlo.sarziputtini@gmail.com (P. Sarzi-Puttini).

https://doi.org/10.1016/j.autrev.2018.12.009
Received 7 December 2018; Accepted 12 December 2018
Available online 05 April 2019
1568-9972/

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-TNFα agents for the treatment of RA

Tumour necrosis factor alpha (TNFα) 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-TNFα 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-TNFα 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-TNFα therapy (Fig. 1), and they will be discussed in the next paragraphs.

1.1.2. Non-anti-TNFα 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 previsous 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

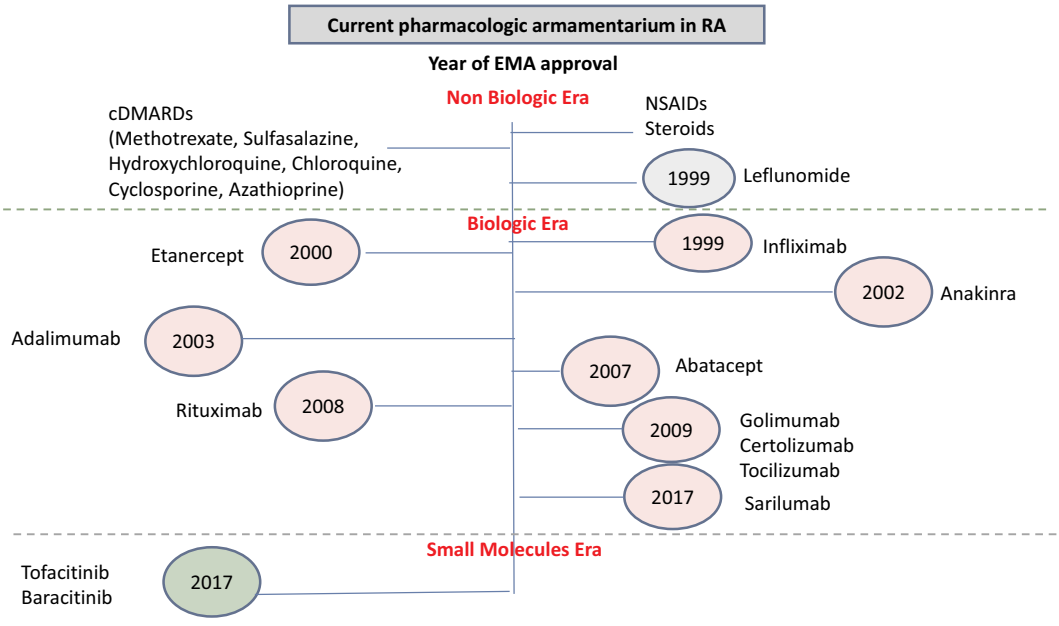

Fig. 1. Current RA pharmacological armamentarium. The name of each drug is given with the year of EMA approval.

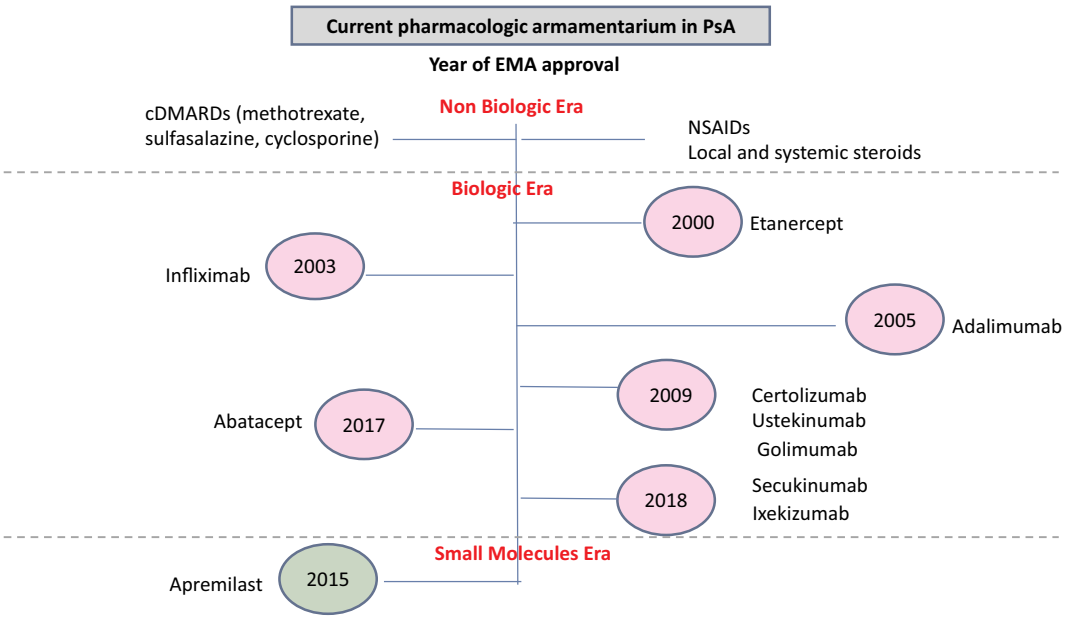

Fig. 2. Current PsA pharmacological armamentarium. The name of each drug is given with the year of EMA approval.

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

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

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	NCT02963506NCT03355573
	SpA		Phase2	NCT02430909
	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	Phase2/3	
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-TNFα 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

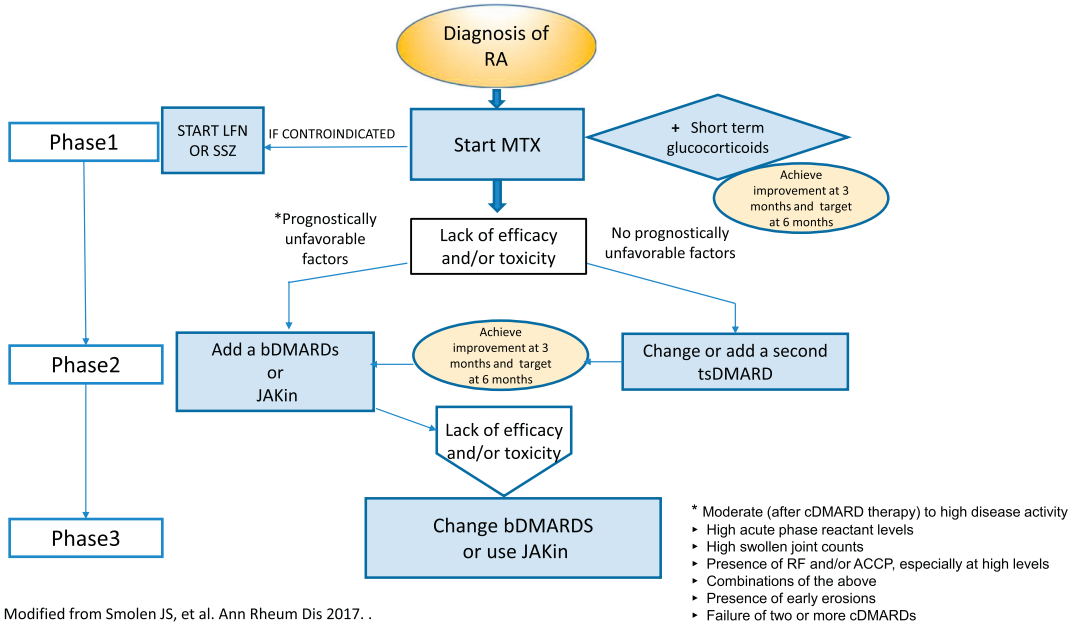

Fig. 3. Schematic illustration of the 2016 EULAR recommendations for the management of RA (modified from Smolen JS, et al. Ann Rheum Dis 2017;76:960–977; [60]).

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. gluococorticoid injections) or start bDMARD treatment with a TNFα 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 ≤4

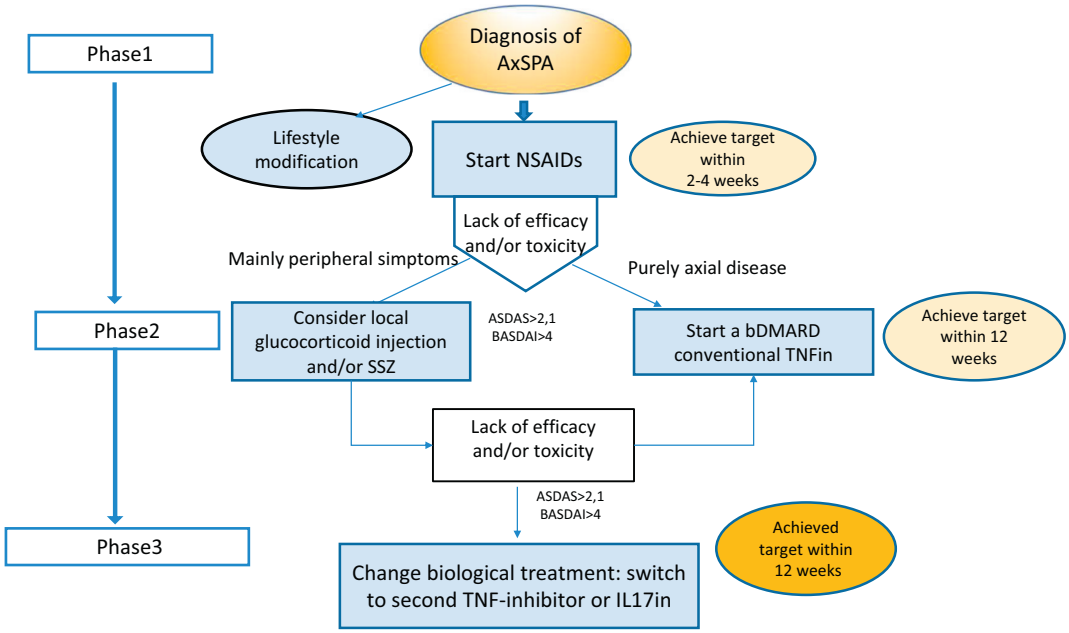

Fig. 4. Schematic illustration of the 2016 EULAR recommendations for the management of AxSpA (modified from Van der Heijde D, et al. Ann Rheum Dis 2017;76:978–991; [88]).

joints) to symmetrical polyarthritis (involving ≥5 joints), with distal inter-phalangeal joints sometimes being the only involved joints. When present, axial disease usually occurs together with peripheral arthritis and, in some rare cases, the arthritis may be rapidly progressive and destructive ("PsA/arthritis mutilans" [79]. PsA affects men and women equally, has a considerable impact on the patients' health-related quality of life, and leads to high healthcare costs and utilisation rates [80,81].

A number of biological drugs for the treatment of PsA are now available on the European pharmacological market (Table 1). Four (infliximab, adalimumab, golimumab, and certolizumab pegol) are monoclonal antibodies that inhibit the activity of TNFα, whereas the fusion protein etanercept and the small molecule apremilast stop the inflammatory process in PsA patients by means of different mechanisms of action (apremilast is a selective inhibitor of PDE4 and, by inhibiting cAMP degradation, lowers the expression of a number of cytokines, including TNFα, IL23 and IL17).

Unfortunately, a subset of PsA patients do not tolerate or satisfactorily respond to these drugs, which is why other biological agents have more recently been approved for the treatment of PsA [82]. Ustekinumab, secukinumab and ixekizumab target and inhibit IL-12/23 (ustekinumab by binding to their common p40 subunit) and IL-17 (secukinumab and ixekizumab), and are now considered second-line treatments. However, their comparative efficacy is unknown as no head-to-head RCTs have yet been conducted. Biological therapies can also be effectively used in specific patient categories such as the elderly and pregnant women, for whom certolizumab pegol has a specific indication because of its proven safety.

The choice of biological agent may be based on the clinical expression of PsA and the extent of PsO and, in the case of primary or failure and infusion reactions, switching or swapping is recommended. As shown in Fig. 5, the EULAR guidelines for active PsA [78] suggest starting with NSAIDs and local glucocorticoid injections (especially in the case of oligoarthritis), then using a cDMARD if this is not efficacious, and finally starting bDMARDs or tsDMARDs in the presence of drug toxicity, unfavorable prognostic factors and/or still active PsA [82]. As patients with active PsA may develop a complex clinical condition with co-morbidities such as diabetes and IBD, and a high risk of infections, the ACR and the National Psoriasis Foundation have developed specific guidelines for their management [83] (Fig. 6).

1.4.4. Updated recommendations for the treatment of RA, AxSpA and PsA

The advent of new biological agents and small molecules has required the updating of the EULAR RA management recommendations [60] in relation to cDMARDs, glucocorticoids, bDMARDs including TNFin (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), abatacept, rituximab, IL-6 inhibitors (tocilizumab and sarilumab), biosimilars and tsDMARDs (the JAK inhibitors tofacitinib and baricitinib) as shown in Fig. 3. The final aim of guidelines in general is the management of rheumatic patients in order to establish monotherapies, combination therapies, treatment strategies (treat-to-target), and the targets of sustained clinical remission (as defined by the ACR/EULAR Boolean or index criteria) [84] and low disease activity.

In the case of SpA, in 2010 two separate sets of recommendations have been released: (1) the international ASAS recommendations for the use of TNFin in patients with axSpA [85]; and (2) the ASAS/EULAR recommendations for the management of AS, which was an update of the first recommendations issued [86]. Since then, many updates (extending also to non-biological therapies) have prompted an effort of ASAS and EULAR to update the recommendations for the management of axSpA [87] which for the first time incorporate the different aspects of management into one set, and also cover the whole spectrum of the disease (Fig. 4). These recommendations apply to patients with radiographic axSpA and to all patients with axSpA also irrespective of the presence of radiographic sacroilitis, and they include a new class of bDMARDs, the IL-17 pathway inhibiting therapy, which recently has become available for the treatment of patients with (radiographic) axSpA. As a first step, there is emphasis on the fact that a proper diagnosis is the starting key point, that such a diagnosis should be made by an expert rheumatologist, and that classification criteria are not enough to make a diagnosis. The 2016 ASAS-EULAR recommendations for the management of axSpA [88] provide a single set of recommendations for the management of patients in the whole spectrum of the disease, including radiographic and non-radiographic axSpA, and they address the whole disease management, both non-pharmacological and pharmacological.

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the EULAR [89] both issued updated

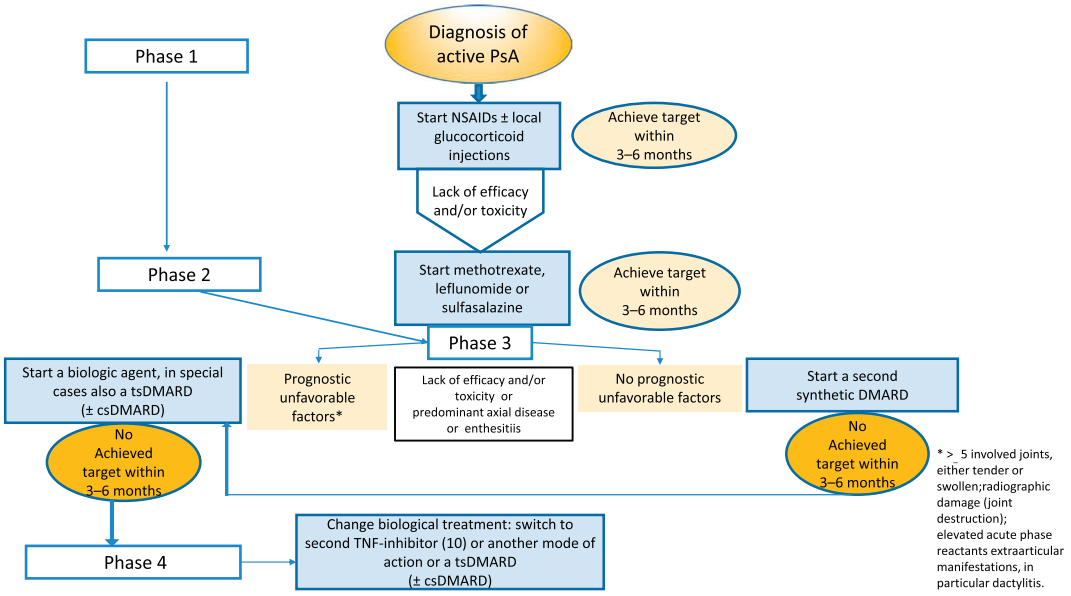

Fig. 5. Schematic illustration of the 2016 EULAR recommendations for the management of active PsA (modified from Gossec L, et al. Ann Rheum Dis. 2016;75:499–510).

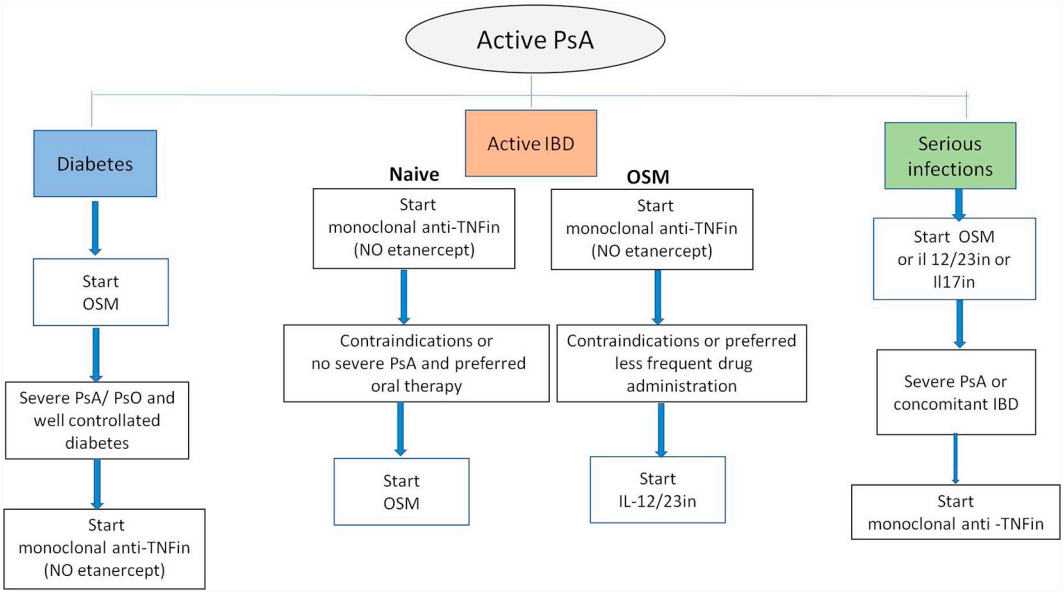

Fig. 6. Schematic illustration of the 2018 ACR/National Psoriasis Foundation Guidelines for the Treatment of Psoriatic Arthritis with co-morbidities (modified from Singh JA, et al. Arthritis Care & Research 2019; 2: 2–29; [83]).

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

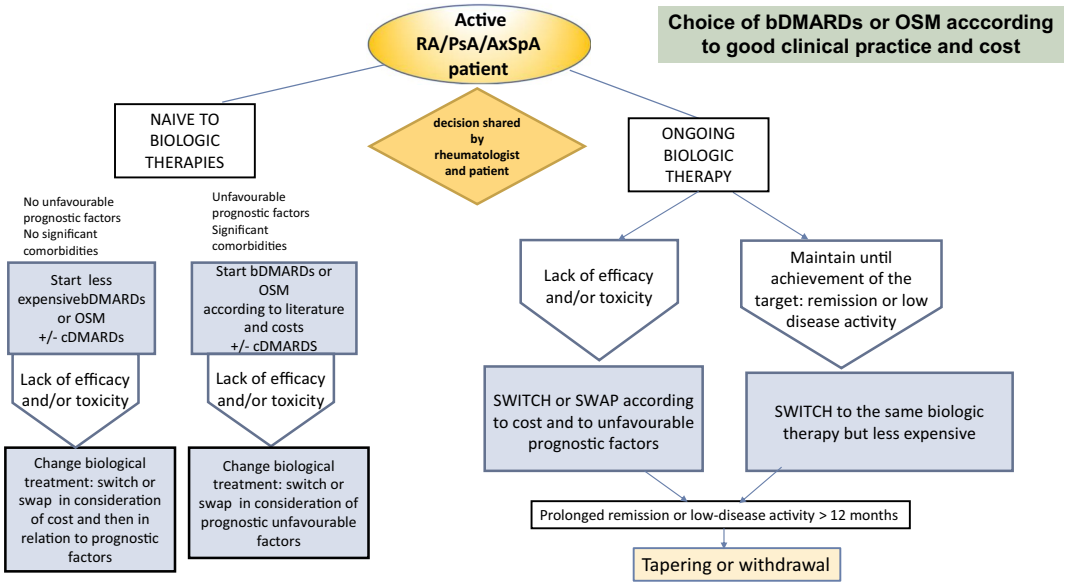

Fig. 7. A possible algorithm for choosing bDMARDs or oral small molecules on the basis of good clinical practice and cost.

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.

References

[1] Pennica D, Nedwin GE, Hayflick JS, Seeburg PH, Derynck R, Palladino MA, et al. Human tumour necrosis factor: precursor structure, expression and homology to lymphotoxin. Nature 1984;312:724–9.
[2] Palladino MA, Bahjat FR, Theodorakis EA, Moldawer LL. Anti-TNF-alpha therapies: the next generation. Nat Rev Drug Discov 2003;2:736–46.
[3] Radner H, Aletaha D. Anti-TNF in rheumatoid arthritis: an overview. Wien Med Wochenschr 2015;165:3–9.
[4] V. Ruiz Garcia, A. Burls, J.B. Cabello, P. Vela Casasempere, S. Bort-Marti and J.A. Bernal, Certolizumab pegol (CDP870) for rheumatoid arthritis in adults, The Cochrane database of systematic reviews 9 (2017) CD007649.
[5] Conti F, Atzeni F, Massaro L, Chiara Gerardi M, Gremese E, Passiu G, et al. The influence of comorbidities on the efficacy of tumour necrosis factor inhibitors, and the effect of tumour necrosis factor inhibitors on comorbidities in rheumatoid arthritis: report from a National Consensus Conference. Rheumatology 2018;57:vii11–22.
[6] Atzeni F, Carletto A, Foti R, Sebastiani M, Panetta V, Salaffi F, et al. Incidence of cancer in patients with spondyloarthritis treated with anti-TNF drugs. Joint Bone Spine 2018;85:455–9.
[7] Atzeni F, Masala IF, di Franco M, Sarzi-Puttini P. Infections in rheumatoid arthritis. Curr Opin Rheumatol 2017;29:323–30.
[8] Cessak G, Kuzawinska O, Burda A, Lis K, Wojnar M, Mirowska-Guzel D, et al. TNF inhibitors - mechanisms of action, approved and off-label indications. Pharmacol Rep 2014;66:836–44.
[9] Rubbert-Roth A, Atzeni F, Masala IF, Caporali R, Montecucco C, Sarzi-Puttini P. TNF inhibitors in rheumatoid arthritis and spondyloarthritis: are they the same? Autoimmun Rev 2018;17:24–8.
[10] Cohen BL, Sachar DB. Update on anti-tumor necrosis factor agents and other new

drugs for inflammatory bowel disease. BMJ 2017;357:j2505.
[11] Caporali R, Crepaldi G, Codullo V, Benaglio F, Monti S, Todoerti M, et al. 20 years of experience with tumour necrosis factor inhibitors: what have we learned? Rheumatology 2018;57:vii5–10.
[12] Moreland L, Bate G, Kirkpatrick P. Abatacept. Nat Rev Drug Discov 2006;5:185–6.
[13] Weisman MH, Durez P, Hallegua D, Aranda R, Becker JC, Nuamah I, et al. Reduction of inflammatory biomarker response by abatacept in treatment of rheumatoid arthritis. J Rheumatol 2006;33:2162–6.
[14] Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 2006;144:865–76.
[15] Ursini F, Russo E, De Giorgio R, De Sarro G, D'Angelo S. Current treatment options for psoriatic arthritis: spotlight on abatacept. Ther Clin Risk Manag 2018;14:1053–9.
[16] Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum 2008;58:2968–80.
[17] Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis 2010;69:88–96.
[18] Rubbert-Roth A, Furst DE, Nebesky JM, Jin A, Berber E. A review of recent advances using tocilizumab in the treatment of rheumatic diseases. Rheumatol Ther 2018;5:21–42.
[19] Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. New England J Med 2004;350:2572–81.
[20] Schioppo T, Ingegnoli F. Current perspective on rituximab in rheumatic diseases. Drug Des Devel Ther 2017;11:2891–904.
[21] Burmester GR, Lin Y, Patel R, van Adelsberg J, Mangan EK, Graham NM, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis 2017;76:840–7.
[22] Abbasi M, Mousavi MJ, Jamalzehi S, Alimohammadi R, Bezvan MH, Mohammadi H, et al. Strategies toward rheumatoid arthritis therapy; the old and the new. J Cell Physiol 2019;234:10018–31.
[23] Cavalli G, Dinarello CA. Anakinra therapy for non-cancer inflammatory diseases. Front Pharmacol 2018;9:1157.
[24] Lubrano E, Perrotta FM. Secukinumab for ankylosing spondylitis and psoriatic arthritis. Ther Clin Risk Manag 2016;12:1587–92.
[25] Weber J, Keam SJ. Ustekinumab. BioDrugs 2009;23:53–61.
[26] Dobbin-Sears I, Roberts J, O'Rielly DD, Rahman P. Ustekinumab in psoriatic arthritis and related phenotypes. Ther Adv Chronic Dis 2018;9:191–8.
[27] Yeilding N, Szapary P, Brodmerkel C, Benson J, Plotnick M, Zhou H, et al. Development of the IL-12/23 antagonist ustekinumab in psoriasis: past, present, and future perspectives–an update. Ann N Y Acad Sci 2012;1263:1–12.
[28] Deepak P, Loftus Jr. EV. Ustekinumab in treatment of Crohn's disease: design, development, and potential place in therapy. Drug Des Devel Ther 2016;10:3685–98.
[29] Shirley M, Scott LJ. Secukinumab: a review in psoriatic arthritis. Drugs 2016;76:1135–45.
[30] Chiricozzi A. Secukinumab in the therapy of psoriasis and psoriatic arthritis: a safe choice in clinical practice. J Dermatolog Treat 2018:1–4.
[31] Kavanaugh A, Marzo-Ortega H, Vender R, Wei CC, Birt J, Adams DH, et al. Ixekizumab improves patient-reported outcomes in patients with active psoriatic arthritis and inadequate response to tumour necrosis factor inhibitors: SPIRIT-P2 results to 52 weeks. Clin Exp Rheumatol 2018. [Epub ahead of print].
[32] Rodig SJ, Meraz MA, White JM, Lampe PA, Riley JK, Arthur CD, et al. Disruption of the Jak1 gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biologic responses. Cell 1998;93:373–83.
[33] Kisseleva T, Bhattacharya S, Braunstein J, Schindler CW. Signaling through the JAK/STAT pathway, recent advances and future challenges. Gene 2002;285:1–24.
[34] Choy EH. Clinical significance of Janus Kinase inhibitor selectivity. Rheumatology (Oxford) 2018. https://doi.org/10.1093/rheumatology/key339. [Epub ahead of print].
[35] Atzeni F, Talotta R, Nucera V, Marino F, Gerratana E, Sangari D, et al. Adverse events, clinical considerations and management recommendations in rheumatoid arthritis patients treated with JAK inhibitors. Expert Rev Clin Immunol 2018;14:945–56.
[36] Caporali R, Zavaglia D. Real-world experience with tofacitinib for treatment of rheumatoid arthritis. Clin Exp Rheumatol 2018. [Epub ahead of print].
[37] Emery P, Pope JE, Kruger K, Lippe R, DeMasi R, Lula S, et al. Efficacy of monotherapy with biologics and JAK inhibitors for the treatment of rheumatoid arthritis: a systematic review. Adv Ther 2018;35:1535–63.
[38] Machado MAA, Moura CS, Guerra SF, Curtis JR, Abrahamowicz M, Bernatsky S. Effectiveness and safety of tofacitinib in rheumatoid arthritis: a cohort study. Arthritis Res Ther 2018;20:60.
[39] Curtis JR, Xie F, Yang S, Bernatsky S, Chen L, Yun H, et al. Herpes zoster in tofacitinib: risk is further increased with glucocorticoids but not methotrexate. Arthritis Care Res (Hoboken) 2018 Oct 8. https://doi.org/10.1002/acr.23769. [Epub ahead of print].
[40] Markham A. Baricitinib: first global approval. Drugs 2017;77:697–704.
[41] van Vollenhoven RF. Small molecular compounds in development for rheumatoid arthritis. Curr Opin Rheumatol 2013;25:391–7.
[42] Huang F, Luo ZC. Risk of adverse drug events observed with baricitinib 2 mg versus baricitinib 4 mg once daily for the treatment of rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. BioDrugs 2018;32:415–23.
[43] Wu ZP, Zhang P, Bai JZ, Liang Y, He JS, Wang JC. Efficacy and safety of baricitinib for active rheumatoid arthritis in patients with an inadequate response to conventional synthetic or biological disease-modifying anti-rheumatic drugs: A meta-analysis of randomized controlled trials. Exp Ther Med 2018;16:2449–59.
[44] Verden A, Dimbil M, Kyle R, Overstreet B, Hoffman KB. Analysis of spontaneous postmarket case reports submitted to the FDA regarding thromboembolic adverse events and JAK inhibitors. Drug Saf 2018;41:357–61.
[45] Scott IC, Hider SL, Scott DL. Thromboembolism with janus kinase (JAK) inhibitors for rheumatoid arthritis: how real is the risk? Drug Saf 2018;41:645–53.
[46] Smolen JS, Genovese MC, Takeuchi T, Hyslop DL, Macias WL, Rooney T, et al. Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. J Rheumatol 2019 Jan;46(1):7–18.
[47] Schett G, Sloan VS, Stevens RM, Schafer P. Apremilast: a novel PDE4 inhibitor in the treatment of autoimmune and inflammatory diseases. Ther Adv Musculoskelet Dis 2010;2:271–8.
[48] Keating GM. Apremilast: a review in psoriasis and psoriatic arthritis. Drugs 2017;77:459–72.
[49] Rich P, Gooderham M, Bachelez H, Goncalves J, Day RM, Chen R, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: Results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). J Am Acad Dermatol 2016;74:134–42.
[50] Qu X, Zhang S, Tao L, Song Y. A meta-analysis of apremilast on psoriatic arthritis long-term assessment of clinical efficacy (PALACE). Expert Rev Clin Pharmacol 2016;9:799–805.
[51] Nash P, Ohson K, Walsh J, Delev N, Nguyen D, Teng L, et al. Early and sustained efficacy with apremilast monotherapy in biological-naive patients with psoriatic arthritis: a phase IIIB, randomised controlled trial (ACTIVE). Ann Rheum Dis 2018;77:690–8.
[52] Crowley J, Thaci D, Joly P, Peris K, Papp KA, Goncalves J, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for > /= 156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). J Am Acad Dermatol 2017;77:310–7.
[53] Zuniga L, Calvo B. Biosimilars approval process. Regul Toxicol Pharmacol 2010;56:374–7.
[54] Kay J, Schoels MM, Dorner T, Emery P, Kvien TK, Smolen JS, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Ann Rheum Dis 2018;77:165–74.
[55] Chadwick L, Zhao S, Mysler E, Moots RJ. Review of biosimilar trials and data on etanercept in rheumatoid arthritis. Curr Rheumatol Rep 2018;20:84.
[56] Reinke T. The biosimilar pipeline seams seem to be bursting. Manag Care 2017;26:24–5.
[57] Bonafede MM, Gandra SR, Watson C, Princic N, Fox KM. Cost per treated patient for etanercept, adalimumab, and infliximab across adult indications: a claims analysis. Adv Ther 2012;29:234–48.
[58] Manova M, Savova A, Vasileva M, Terezova S, Kamusheva M, Grekova D, et al. Comparative price analysis of biological products for treatment of rheumatoid arthritis. Front Pharmacol 2018;9:1070.
[59] Majithia V, Geraci SA. Rheumatoid arthritis: diagnosis and management. Am J Med 2007;120:936–9.
[60] Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.
[61] Batticciotto A, Ravasio R, Riva M, Sarzi-Puttini P. Efficacy and treatment costs of monotherapy with bDMARDs in the treatment of rheumatoid arthritis in patients intolerant to or inappropriate to continue treatment with methotrexate. Adv Ther 2016;33:1360–73.
[62] Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.
[63] Singh JA, Saag KG, Bridges Jr. SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American college of rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res 2016;68:1–25.
[64] Favalli EG, Sinigaglia L, Becciolini A, Grosso V, Gorla R, Bazzani C, et al. Two-year persistence of golimumab as second-line biologic agent in rheumatoid arthritis as compared to other subcutaneous tumor necrosis factor inhibitors: real-life data from the LORHEN registry. Int J Rheum Dis 2018;21:422–30.
[65] Elmamoun M, Chandran V. Role of methotrexate in the management of psoriatic arthritis. Drugs 2018;78:611–9.
[66] Favalli EG, Biggioggero M, Marchesoni A, Meroni PL. Survival on treatment with second-line biologic therapy: a cohort study comparing cycling and swap strategies. Rheumatology 2014;53:1664–8.
[67] Todoerti M, Favalli EG, Iannone F, Olivieri I, Benucci M, Cauli A, et al. Switch or swap strategy in rheumatoid arthritis patients failing TNF inhibitors? Results of a modified Italian Expert Consensus. Rheumatology 2018;57:vii42–53.
[68] Favalli EG, Raimondo MG, Becciolini A, Crotti C, Biggioggero M, Caporali R. The management of first-line biologic therapy failures in rheumatoid arthritis: current practice and future perspectives. Autoimmun Rev 2017;16:1185–95.
[69] Iannone F, Ferraccioli G, Sinigaglia L, Favalli EG, Sarzi-Puttini P, Atzeni F, et al. Real-world experience of tocilizumab in rheumatoid arthritis: sub-analysis of data from the Italian biologics' register GISEA. Clin Rheumatol 2018;37:315–21.
[70] Ye W, Tucker LJ, Coates LC. Tapering and discontinuation of biologics in patients

with psoriatic arthritis with low disease activity. Drugs 2018;78:1705–15.
[71] Atzeni F, Benucci M, Talotta R, Masala IF, Sarzi-Puttini P, Govoni M. What are the dangers of biological therapy discontinuation or dose reduction strategies when treating rheumatoid arthritis? Expert Rev Clin Pharmacol 2016;9:1403–11.
[72] Luong AA, Salonen DC. Imaging of the seronegative spondyloarthropathies. Curr Rheumatol Rep 2000;2:288–96.
[73] D'Agostino MA, Olivieri I. Enthesitis. Best Pract Res Clin Rheumatol 2006;20:473–86.
[74] Rizzo A, Ferrante A, Guggino G, Ciccia F. Gut inflammation in spondyloarthritis. Best Pract Res Clin Rheumatol 2017;31:863–76.
[75] Chen B, Li J, He C, Li D, Tong W, Zou Y, et al. Role of HLA-B27 in the pathogenesis of ankylosing spondylitis (review). Mol Med Rep 2017;15:1943–51.
[76] Luchetti MM, Benfaremo D, Gabrielli A. Biologics in inflammatory and immunomediated arthritis. Curr Pharm Biotechnol 2017;18:989–1007.
[77] Benucci M, Damiani A, Bandinelli F, Grossi V, Infantino M, Manfredi M, et al. Ankylosing spondylitis treatment after first anti-TNF drug failure. Isr Med Assoc J 2018;20:119–22.
[78] Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis 2016;75:499–510.
[79] Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet 2018;391:2273–84.
[80] Kruntoradova K, Klimes J, Sedova L, Stolfa J, Dolezal T, Petrikova A. Work productivity and costs related to patients with ankylosing spondylitis, rheumatoid arthritis, and psoriasis. Value Health Reg Issue 2014;4:100–6.
[81] Evans C. Managed care aspects of psoriasis and psoriatic arthritis. Am J Manag Care 2016;22:s238–43.
[82] Kawalec P, Holko P, Mocko P, Pilc A. Comparative effectiveness of abatacept, apremilast, secukinumab and ustekinumab treatment of psoriatic arthritis: a systematic review and network meta-analysis. Rheumatol Int 2018;38:189–201.
[83] Singh JA, Guyatt G, Ogdie A, Gladman DD, Deal C, Deodhar A, et al. Special article: 2018 American college of rheumatology/national psoriasis foundation guideline for the treatment of psoriatic arthritis. Arthritis Care Res 2019;71:2–29.
[84] Bykerk VP, Massarotti EM. The new ACR/EULAR remission criteria: rationale for developing new criteria for remission. Rheumatology 2012;51(Suppl. 6):vi16–20.
[85] van der Heijde D, Sieper J, Maksymowych WP, Dougados M, Burgos-Vargas R, Landewe R, et al. 2010 update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70:905–8.
[86] Braun J, Pham T, Sieper J, Davis J, van der Linden S, Dougados M, et al. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. Ann Rheum Dis 2003;62:817–24.
[87] Sepriano A, Regel A, van der Heijde D, Braun J, Baraliakos X, Landewe R, et al. Efficacy and safety of biological and targeted-synthetic DMARDs: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. RMD Open 2017;3:e000396.
[88] van der Heijde D, Ramiro S, Landewe R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978–91.
[89] Coates LC, Gossec L, Ramiro S, Mease P, van der Heijde D, Smolen JS, et al. New GRAPPA and EULAR recommendations for the management of psoriatic arthritis. Rheumatology 2017;56:1251–3.
[90] Mahmood F, Coates LC, Helliwell PS. Current concepts and unmet needs in psoriatic arthritis. Clin Rheumatol 2018;37:297–305.
[91] Atzeni F, Talotta R, Masala IF, Bongiovanni S, Boccassini L, Sarzi-Puttini P. Biomark Rheumat Arthrit 2017;19:512–6.
[92] Cantini F, Niccoli L, Nannini C, Cassara E, Kaloudi O, Favalli E Giulio, et al. Tailored first-line biologic therapy in patients with rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis. Semin Arthritis Rheum 2016;45:519–32.
[93] Monti S, Klersy C, Gorla R, Sarzi-Puttini P, Atzeni F, Pellerito R, et al. Factors influencing the choice of first- and second-line biologic therapy for the treatment of rheumatoid arthritis: real-life data from the Italian LORHEN Registry. Clin Rheumatol 2017;36:753–61.
[94] van Riel P, Alten R, Combe B, Abdulganieva D, Bousquet P, Courtenay M, et al. Improving inflammatory arthritis management through tighter monitoring of patients and the use of innovative electronic tools. RMD Open 2016;2:e000302.
[95] van der Linden MP, Knevel R, Huizinga TW, van der Helm-van Mil AH. Classification of rheumatoid arthritis: comparison of the 1987 American College of Rheumatology criteria and the 2010 American College of Rheumatology/European League Against Rheumatism criteria. Arthritis Rheum 2011;63:37–42.
[96] Fleischmann R, Connolly SE, Maldonado MA, Schiff M. Brief report: estimating disease activity using multi-biomarker disease activity scores in rheumatoid arthritis patients treated with abatacept or adalimumab. Arthritis Rheum 2016;68:2083–9.
[97] Cantini F, Benucci M. Switching from the bio-originators to biosimilar: is it premature to recommend this procedure? Ann Rheum Dis 2019 Apr;78(4):e23.
[98] Marchesoni A, Olivieri I, Salvarani C, Pipitone N, D'Angelo S, Mathieu A, et al. Recommendations for the use of biologics and other novel drugs in the treatment of psoriatic arthritis: 2017 update from the Italian Society of Rheumatology. Clin Exp Rheumatol 2017;35:991–1010.
[99] Rezk MF, Pieper B. Treatment outcomes with biosimilars: be aware of the Nocebo effect. Rheumatol Ther 2017;4:209–18.