Accepted Manuscript

Systemic rheumatic diseases: From biological agents to small molecules

Piercarlo Sarzi-Puttini, Angela Ceribelli, Daniela Marotto, Alberto Batticciotto, Fabiola Atzeni

PII: S1568-9972(19)30087-4
DOI: https://doi.org/10.1016/j.autrev.2018.12.009
Reference: AUTREV 2319

To appear in: *Autoimmunity Reviews*

Received date: 7 December 2018
Accepted date: 12 December 2018

Please cite this article as: P. Sarzi-Puttini, A. Ceribelli, D. Marotto, et al., Systemic rheumatic diseases: From biological agents to small molecules, Autoimmunity Reviews, https://doi.org/10.1016/j.autrev.2018.12.009

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

SYSTEMIC RHEUMATIC DISEASES: FROM BIOLOGICAL AGENTS TO SMALL MOLECULES

Piercarlo Sarzi-Puttini[a,*] piercarlo.sarziputtini@gmail.com, 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

[*]Corresponding author at: Rheumatology Unit, ASST Fatebenefratelli-Sacco, University of Milan, Via GB Grassi 74, 20157 Milano, Italy.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

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 institututions, such as those for Rheumatoid Arthritis treatment that address the use of conventional and biologic therapies including TNFin (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-stroidal 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. gluococorticoid injections) or to start biologic therapy such as TNFin and then eventually switching to another TNFin or swapping to IL17in. 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.

Keywords: Biological therapies; biosimilars; rheumatoid arthritis; spondyloartropathies; psoriatic arthritis; small molecules; guidelines; recommendations.

Abbreviations

ANCAs anti-neutrophil cytoplasmic antibodies

AxSpa ankylosing spondylitis

BD Behçet's disease

ACCEPTED MANUSCRIPT

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

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

ACCEPTED MANUSCRIPT

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 of these molecules are monoclonal antibodies (mAbs) or fragments of mAbs: infliximab is a chimeric mouse/human anti-TNFα mAb consisting of a variable murine region and a constant human IgG1 region; adalimumab and golimumab are fully humanised anti-TNFα mAbs that cannot be distinguished from normal human IgG1; etanercept is a fusion protein consisting of the two extra-cellular portions of human TNF receptor 2 (p75 TNF receptor) and the Fc portion (hinge, CH2 and CH3 domains) of human IgG1; and certolizumab is a Fab' fragment of an anti-TNFα mAb lacking the Fc portion (its hinge region is covalently linked to two 20 kDa cross-linked chains of polyethylene glycol, which is why it is called certolizumab pegol) (**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, ankylosing spondyloarthritis (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 of the soluble etanercept [10].

ACCEPTED MANUSCRIPT

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 have been developed and approved for treatment in the case of the failure of anti-TNFα therapy (**Fig. 1**). The class of anti-TNFα therapies has proved to be the most used since 2000, and it is currently available for the treatment of several rheumatic diseases, not only in the adult but also in the pediatric patients (i.e. uveitis, IBD, SpA, PsA, RA, juvenile arthritis).

1.1.2 Non-anti-TNFα biological agents for the treatment of RA

Various biological drugs 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]. Phase III trials have shown that both i.v. and s.c. regimens have beneficial effects on signs and symptoms, disease activity, structural damage progression and physical function, particularly when combined with MTX [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, tocilizumab leads to a rapid and sustained improvement in clinical and radiographic outcomes and the health-related quality of life [17], and its safety profile is consistent over time and similar to that of other immunomodulatory agents. There is a low risk of immunogenicity, and both the flexibility of having two possible routes of administration, and the convenience of the once-weekly, self-administered s.c. regimen allow the effective treatment of severe, active and progressive RA in adults. Tocilizumab can be used in RA patients not previously treated with MTX, and is an effective first-line or subsequent biological treatment for adults with moderate to severe active RA inadequately responding to or intolerant of previous treatment with ≥1 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

ACCEPTED MANUSCRIPT

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-IL6 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 MYX (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 is also used to treat other indications [22], insofar as 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, 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 Tab. 1**).

Ustekinumab is a fully human immunoglobulin(Ig)G1 mAb that specifically binds to the p40 subunit of IL12 and IL23, thus inhibiting the Th17 signalling pathways downstream. It has proved to be clinically efficacious for up to 52 weeks in two phase III trials involving PsA patients (PSUMMIT-1 and PSUMMIT-2) [26], neither of which detected any safety concerns. PSUMMIT-1 enrolled patients with active PsA despite conventional therapy who were all naïve to anti-TNFα agents, whereas PSUMMIT-2 also included patients who had anti-TNFα agents. It also proved to be clinically efficacious in two phase III clinical trials involving PsO patients (PHOENIX-1 and PHOENIX-2) [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].

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] (**Tab. 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.

ACCEPTED MANUSCRIPT

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] (**Tab. 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 use specific JAK isoforms for intracellular signal transduction. JAK phosphorylates cytokine-bound receptors, and this triggers the intra-cellular 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 (**Tab. 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 lasting for less than two years have shown that tofacitinib alone (as first or second line treatment) or combined with a cDMARD is effective in reducing RA signs and symptoms of RA, and improves health-related quality of life during long-term therapy [37]. It has generally been well tolerated: most of the observed adverse events have been mild or moderately severe and are similar to those related to biological drugs, particularly infections [38]. One specific alert has been issued because of the risk of herpes zoster infection in tofacitinib-treated patients, even though the observed cases have been clinically mild [39].

Baricitinib is a selective and reversible oral inhibitor of JAK1 and JAK2 [40] that has significantly improved the histological and radiographic signs of RA in pre-clinical animal models of arthritis, with no evidence of suppressed humoral immunity or adverse hematological effects [41]. The positive results also obtained in phase II and III clinical trials [42], has lead to two doses (2 and 4 mg/day) being approved in the EU and Japan for the treatment of moderate-severe RA in patients inadequately responding to cDMARDs, alone or in combination with MTX [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

ACCEPTED MANUSCRIPT

Apremilast is an orally administered small molecule that inhibits phosphodiesterase 4 (PDE4) [47, 48]. It was approved by the FDA in 2014 and by the EMA in 2015 (**Tab. 1**) at a dose of 30 mg twice daily after it had been demonstrated that it reduced the severity of moderate to severe plaque PsO in the phase III 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

The last few years have seen the increasing use of biosimilars in rheumatology as a result of the expiry of the patents protecting traditional biological drugs. Biosimilars are highly similar copies of originator biological drugs that are approved after they have undergone rigorous physico-chemical, non-clinical and clinical evaluations, and pre-defined and stringent regulatory processes [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], the biosimilar of rituximab has recently been approved for use in RA patients, and there are a number of other biosimilars in the pipeline [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.

2.1 TREATMENT GUIDELINES

2.1.1 Rheumatoid arthritis

RA is a chronic, autoimmune, systemic inflammatory disorder that symmetrically affects small and large synovial joints, and significantly reduces patients' quality of life and life expectancy if left untreated. The

ACCEPTED MANUSCRIPT

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 the case of incomplete responders to MTX (MTX-IRs), neither the EULAR nor the ACR recommendations indicate the use of a specific bDMARD or tsDMARD or suggest a treatment sequence [62-64]: there are few studies directly comparing bDMARDs with different modes of action in combination with MTX, and indirect comparisons strongly suggest that all bDMARDs are similarly efficacious when used in combination with MTX. Generally, bDMARDs are used in combination with MTX but, as more than one-third of patients are intolerant to MTX and adherence is often poor (especially when administered orally), about 30% of patients are treated with a bDMARD alone in clinical practice [65].

There is still disagreement concerning the best way of managing RA patients who inadequately respond to their first TNFin (TNF-Irs): the ACR recommends using a non-TNF biological drug [63], whereas the EULAR recommends a second TNF inhibitor or agent with a different mode of action (so-called “swapping”) [60], which is also supported by observational data [66,67]. Patients with a secondary inadequate response to a TNFin may have developed anti-drug antibodies, and such patients can be expected to respond to an antigenically distinct drug.

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].

2.1.2 Spondyloarthropathies (SpAs)

Spondyloarthropathies (SpAs) are a family of chronic rheumatic conditions characterised 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

ACCEPTED MANUSCRIPT

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]. However, although this approach has proved to be efficacious, TNFin treatment may not induce clinical remission in a substantial proportion of patients. This has prompted a search for drugs with alternative mechanisms of action [77], and has lead to other biological agents being approved or investigated [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**).

2.1.3 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 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 (**Tab. 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

ACCEPTED MANUSCRIPT

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 **Figure 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, unfavourable 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**).

2.1.4 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 **Figure 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.

Two separate sets of recommendations concerning SpA were released in 2010: 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 updated the previously issued recommendations [86]. Since then, many updates extended to include non-biological therapies have prompted an effort by the ASAS and EULAR to update their recommendations for the management of axSpA [87] which, for the first time, incorporate the different aspects of management into one set of recommendations covering the entire disease spectrum (**Fig. 4**). These recommendations apply to patients with radiographic AxSpA and all patients with AxSpA regardless of the presence of radiographic sacroilitis, and include the new bDMARD class of IL-17 pathway inhibitors. There is an emphasis on the fact that a correct diagnosis is essential and should be made by an expert rheumatologist, and that classification criteria are not diagnostically sufficient. The 2016 ASAS-EULAR recommendations for the management of AxSpA [88] include radiographic and non-radiographic AxSpA, and address both pharmacological and non-pharmacological disease management.

ACCEPTED MANUSCRIPT

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

2.1.5 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, researches 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 le to any 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 peripheral 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 rationalise 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

ACCEPTED MANUSCRIPT

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.

Figure 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.

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.

ACCEPTED MANUSCRIPT

REFERENCES

[1] D. Pennica, G.E. Nedwin, J.S. Hayflick, P.H. Seeburg, R. Derynck, M.A. Palladino, W.J. Kohr, B.B. Aggarwal and D.V. Goeddel, Human tumour necrosis factor: precursor structure, expression and homology to lymphotoxin, Nature 312 (1984) 724-9.

[2] M.A. Palladino, F.R. Bahjat, E.A. Theodorakis and L.L. Moldawer, Anti-TNF-alpha therapies: the next generation, Nature reviews. Drug discovery 2 (2003) 736-46.

[3] H. Radner and D. Aletaha, Anti-TNF in rheumatoid arthritis: an overview, Wiener medizinische Wochenschrift 165 (2015) 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] F. Conti, F. Atzeni, L. Massaro, M. Chiara Gerardi, E. Gremese, G. Passiu, A. Carletto, N. Malavolta, R. Foti, R. Ramonda and P. Sarzi-Puttini, 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 57 (2018) vii11-vii22.

[6] F. Atzeni, A. Carletto, R. Foti, M. Sebastiani, V. Panetta, F. Salaffi, G. Bonitta, F. Iannone, E. Gremese, M. Govoni, A. Marchesoni, E.G. Favalli, R. Gorla, R. Ramonda, P. Sarzi-Puttini, G. Ferraccioli, G. Lapadula and G. group, Incidence of cancer in patients with spondyloarthritis treated with anti-TNF drugs. Joint, bone, spine : revue du rhumatisme 85 (2018) 455-459.

[7] F. Atzeni, I.F. Masala, M. di Franco and P. Sarzi-Puttini, Infections in rheumatoid arthritis, Curr Opin Rheumatol 29 (2017) 323-330.

[8] G. Cessak, O. Kuzawinska, A. Burda, K. Lis, M. Wojnar, D. Mirowska-Guzel and E. Balkowiec-Iskra, TNF inhibitors - Mechanisms of action, approved and off-label indications, Pharmacological reports : PR 66 (2014) 836-44.

[9] A. Rubbert-Roth, F. Atzeni, I.F. Masala, R. Caporali, C. Montecucco and P. Sarzi-Puttini, TNF inhibitors in rheumatoid arthritis and spondyloarthritis: Are they the same?, Autoimmun Rev 17 (2018) 24-28.

[10] B.L. Cohen and D.B. Sachar, Update on anti-tumor necrosis factor agents and other new drugs for inflammatory bowel disease, BMJ 357 (2017) j2505.

[11] R. Caporali, G. Crepaldi, V. Codullo, F. Benaglio, S. Monti, M. Todoerti and C. Montecucco, 20 years of experience with tumour necrosis factor inhibitors: what have we learned?, Rheumatology 57 (2018) vii5-vii10.

[12] L. Moreland, G. Bate and P. Kirkpatrick, Abatacept, Nat Rev Drug Discov 5 (2006) 185-6.

[13] M.H. Weisman, P. Durez, D. Hallegua, R. Aranda, J.C. Becker, I. Nuamah, G. Vratsanos, Y. Zhou and L.W. Moreland, Reduction of inflammatory biomarker response by abatacept in treatment of rheumatoid arthritis, J Rheumatol 33 (2006) 2162-6.

[14] J.M. Kremer, H.K. Genant, L.W. Moreland, A.S. Russell, P. Emery, C. Abud-Mendoza, J. Szechinski, T. Li, Z. Ge, J.C. Becker and R. Westhovens, Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial, Ann Intern Med 144 (2006) 865-76.

[15] F. Ursini, E. Russo, R. De Giorgio, G. De Sarro and S. D'Angelo, Current treatment options for psoriatic arthritis: spotlight on abatacept. Ther Clin Risk Manag 14 (2018) 1053-1059.

[16] M.C. Genovese, J.D. McKay, E.L. Nasonov, E.F. Mysler, N.A. da Silva, E. Alecock, T. Woodworth and J.J. Gomez-Reino, 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 58 (2008) 2968-80.

[17] G. Jones, A. Sebba, J. Gu, M.B. Lowenstein, A. Calvo, J.J. Gomez-Reino, D.A. Siri, M. Tomsic, E. Alecock, T. Woodworth and M.C. Genovese, Comparison of tocilizumab

ACCEPTED MANUSCRIPT

monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study, Ann Rheum Dis 69 (2010) 88-96.

[18] A. Rubbert-Roth, D.E. Furst, J.M. Nebesky, A. Jin and E. Berber, A Review of Recent Advances Using Tocilizumab in the Treatment of Rheumatic Diseases. Rheumatol Ther 5 (2018) 21-42.

[19] J.C. Edwards, L. Szczepanski, J. Szechinski, A. Filipowicz-Sosnowska, P. Emery, D.R. Close, R.M. Stevens and T. Shaw, Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis, New England J Med 350 (2004) 2572-81.

[20] T. Schioppo and F. Ingegnoli, Current perspective on rituximab in rheumatic diseases, Drug design, development and therapy 11 (2017) 2891-2904.

[21] G.R. Burmester, Y. Lin, R. Patel, J. van Adelsberg, E.K. Mangan, N.M. Graham, H. van Hoogstraten, D. Bauer, J. Ignacio Vargas and E.B. Lee, 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 76 (2017) 840-847.

[22] M. Abbasi, M.J. Mousavi, S. Jamalzehi, R. Alimohammadi, M.H. Bezvan, H. Mohammadi and S. Aslani, Strategies toward rheumatoid arthritis therapy; the old and the new, J Cell Physiol (2018).

[23] G. Cavalli and C.A. Dinarello, Anakinra Therapy for Non-cancer Inflammatory Diseases, Front Pharmacol 9 (2018) 1157.

[24] E. Lubrano and F.M. Perrotta, Secukinumab for ankylosing spondylitis and psoriatic arthritis, Ther Clin Risk Manag 12 (2016) 1587-1592.

[25] J. Weber and S.J. Keam, Ustekinumab, BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy 23 (2009) 53-61.

[26] I. Dobbin-Sears, J. Roberts, D.D. O'Rielly and P. Rahman, Ustekinumab in psoriatic arthritis and related phenotypes, Ther Adv Chronic Dis 9 (2018) 191-198.

[27] N. Yeilding, P. Szapary, C. Brodmerkel, J. Benson, M. Plotnick, H. Zhou, K. Goyal, B. Schenkel, J. Giles-Komar, M.A. Mascelli and C. Guzzo, Development of the IL-12/23 antagonist ustekinumab in psoriasis: past, present, and future perspectives--an update, Ann NY Acad Sci 1263 (2012) 1-12.

[28] P. Deepak and E.V. Loftus, Jr., Ustekinumab in treatment of Crohn's disease: design, development, and potential place in therapy, Drug design, development and therapy 10 (2016) 3685-3698.

[29] M. Shirley and L.J. Scott, Secukinumab: A Review in Psoriatic Arthritis, Drugs 76 (2016) 1135-45.

[30] A. Chiricozzi, Secukinumab in the therapy of psoriasis and psoriatic arthritis: a safe choice in clinical practice. J Dermatolog Treat (2018) 1-4.

[31] A. Kavanaugh, H. Marzo-Ortega, R. Vender, C.C. Wei, J. Birt, D.H. Adams, O. Benichou, C.Y. Lin and P. Nash, 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, Clinical Exp Rheumatol (2018).

[32] S.J. Rodig, M.A. Meraz, J.M. White, P.A. Lampe, J.K. Riley, C.D. Arthur, K.L. King, K.C. Sheehan, L. Yin, D. Pennica, E.M. Johnson, Jr. and R.D. Schreiber, Disruption of the Jak1 gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biologic responses, Cell 93 (1998) 373-83.

[33] T. Kisseleva, S. Bhattacharya, J. Braunstein and C.W. Schindler, Signaling through the JAK/STAT pathway, recent advances and future challenges, Gene 285 (2002) 1-24.

[34] E.H. Choy, Clinical significance of Janus Kinase inhibitor selectivity, Rheumatology (2018).

[35] F. Atzeni, R. Talotta, V. Nucera, F. Marino, E. Gerratana, D. Sangari, I.F. Masala and P. Sarzi-Puttini, Adverse events, clinical considerations and management recommendations in

ACCEPTED MANUSCRIPT

rheumatoid arthritis patients treated with JAK inhibitors, Expert Rev Clin Immunol 14 (2018) 945-956.

[36] R. Caporali and D. Zavaglia, Real-world experience with tofacitinib for treatment of rheumatoid arthritis, Clinical Exp Rheumatol (2018).

[37] P. Emery, J.E. Pope, K. Kruger, R. Lippe, R. DeMasi, S. Lula and B. Kola, Efficacy of Monotherapy with Biologics and JAK Inhibitors for the Treatment of Rheumatoid Arthritis: A Systematic Review, Adv Ther 35 (2018) 1535-1563.

[38] M.A.A. Machado, C.S. Moura, S.F. Guerra, J.R. Curtis, M. Abrahamowicz and S. Bernatsky, Effectiveness and safety of tofacitinib in rheumatoid arthritis: a cohort study, Arthritis Res Ther 20 (2018) 60.

[39] J.R. Curtis, F. Xie, S. Yang, S. Bernatsky, L. Chen, H. Yun and K. Winthrop, Herpes Zoster in Tofacitinib: Risk is Further Increased with Glucocorticoids but not Methotrexate, Arthritis Care Res (2018).

[40] A. Markham, Baricitinib: First Global Approval, Drugs 77 (2017) 697-704.

[41] R.F. van Vollenhoven, Small molecular compounds in development for rheumatoid arthritis, Current Opin Rheumatol 25 (2013) 391-7.

[42] F. Huang and Z.C. Luo, 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 : clinical immunotherapeutics, biopharmaceuticals and gene therapy 32 (2018) 415-423.

[43] Z.P. Wu, P. Zhang, J.Z. Bai, Y. Liang, J.S. He and J.C. Wang, 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. 16 (2018) 2449-2459.

[44] A. Verden, M. Dimbil, R. Kyle, B. Overstreet and K.B. Hoffman, Analysis of Spontaneous Postmarket Case Reports Submitted to the FDA Regarding Thromboembolic Adverse Events and JAK Inhibitors, Drug safety 41 (2018) 357-361.

[45] I.C. Scott, S.L. Hider and D.L. Scott, Thromboembolism with Janus Kinase (JAK) Inhibitors for Rheumatoid Arthritis: How Real is the Risk?, Drug safety 41 (2018) 645-653.

[46] J.S. Smolen, M.C. Genovese, T. Takeuchi, D.L. Hyslop, W.L. Macias, T. Rooney, L. Chen, C.L. Dickson, J. Riddle Camp, T.E. Cardillo, T. Ishii and K.L. Winthrop, Safety Profile of Baricitinib in Patients with Active Rheumatoid Arthritis with over 2 Years Median Time in Treatment, J Rheumatol (2018).

[47] G. Schett, V.S. Sloan, R.M. Stevens and P. Schafer, Apremilast: a novel PDE4 inhibitor in the treatment of autoimmune and inflammatory diseases, Ther Adv Musculoskelet Dis 2 (2010) 271-8.

[48] G.M. Keating, Apremilast: A Review in Psoriasis and Psoriatic Arthritis, Drugs 77 (2017) 459-472.

[49] P. Rich, M. Gooderham, H. Bachelez, J. Goncalves, R.M. Day, R. Chen and J. Crowley, 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 74 (2016) 134-42.

[50] X. Qu, S. Zhang, L. Tao and Y. Song, A meta-analysis of apremilast on psoriatic arthritis long-term assessment of clinical efficacy (PALACE), Expert Rev Clin Pharmacol 9 (2016) 799-805.

[51] P. Nash, K. Ohson, J. Walsh, N. Delev, D. Nguyen, L. Teng, J.J. Gomez-Reino, J.A. Aelion and A. investigators, Early and sustained efficacy with apremilast monotherapy in biological-naive patients with psoriatic arthritis: a phase IIIB, randomised controlled trial (ACTIVE), Ann Rheum Dis 77 (2018) 690-698.

[52] J. Crowley, D. Thaci, P. Joly, K. Peris, K.A. Papp, J. Goncalves, R.M. Day, R. Chen, K. Shah, C. Ferrandiz and J.C. Cather, Long-term safety and tolerability of apremilast in

ACCEPTED MANUSCRIPT

patients with psoriasis: Pooled safety analysis for >/=156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2), J Am Acad Dermatol 77 (2017) 310-317 e1.

[53] L. Zuniga and B. Calvo, Biosimilars approval process, Regulatory toxicology and pharmacology : RTP 56 (2010) 374-7.

[54] J. Kay, M.M. Schoels, T. Dorner, P. Emery, T.K. Kvien, J.S. Smolen, F.C. Breedveld and D. Task Force on the Use of Biosimilars to Treat Rheumatological, Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases, Annals of the rheumatic diseases 77 (2018) 165-174.

[55] L. Chadwick, S. Zhao, E. Mysler and R.J. Moots, Review of Biosimilar Trials and Data on Etanercept in Rheumatoid Arthritis, Current rheumatology reports 20 (2018) 84.

[56] T. Reinke, The Biosimilar Pipeline Seams Seem To Be Bursting, Managed care 26 (2017) 24-25.

[57] M.M. Bonafede, S.R. Gandra, C. Watson, N. Princic and K.M. Fox, Cost per treated patient for etanercept, adalimumab, and infliximab across adult indications: a claims analysis, Adv Ther 29 (2012) 234-48.

[58] M. Manova, A. Savova, M. Vasileva, S. Terezova, M. Kamusheva, D. Grekova, V. Petkova and G. Petrova, Comparative Price Analysis of Biological Products for Treatment of Rheumatoid Arthritis, Front Pharmacol 9 (2018) 1070.

[59] V. Majithia and S.A. Geraci, Rheumatoid arthritis: diagnosis and management. Am J Med 120 (2007) 936-9.

[60] J.S. Smolen, R. Landewe, J. Bijlsma, G. Burmester, K. Chatzidionysiou, M. Dougados, J. Nam, S. Ramiro, M. Voshaar, R. van Vollenhoven, D. Aletaha, M. Aringer, M. Boers, C.D. Buckley, F. Buttgereit, V. Bykerk, M. Cardiel, B. Combe, M. Cutolo, Y. van Eijk-Hustings, P. Emery, A. Finckh, C. Gabay, J. Gomez-Reino, L. Gossec, J.E. Gottenberg, J.M.W. Hazes, T. Huizinga, M. Jani, D. Karateev, M. Kouloumas, T. Kvien, Z. Li, X. Mariette, I. McInnes, E. Mysler, P. Nash, K. Pavelka, G. Poor, C. Richez, P. van Riel, A. Rubbert-Roth, K. Saag, J. da Silva, T. Stamm, T. Takeuchi, R. Westhovens, M. de Wit and D. van der Heijde, EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update, Ann Rheum Dis 76 (2017) 960-977.

[61] A. Batticciotto, R. Ravasio, M. Riva and P. Sarzi-Puttini, 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 33 (2016) 1360-73.

[62] J.S. Smolen, R. Landewe, F.C. Breedveld, M. Buch, G. Burmester, M. Dougados, P. Emery, C. Gaujoux-Viala, L. Gossec, J. Nam, S. Ramiro, K. Winthrop, M. de Wit, D. Aletaha, N. Betteridge, J.W. Bijlsma, M. Boers, F. Buttgereit, B. Combe, M. Cutolo, N. Damjanov, J.M. Hazes, M. Kouloumas, T.K. Kvien, X. Mariette, K. Pavelka, P.L. van Riel, A. Rubbert-Roth, M. Scholte-Voshaar, D.L. Scott, T. Sokka-Isler, J.B. Wong and D. van der Heijde, EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update, Ann Rheum Dis 73 (2014) 492-509.

[63] J.A. Singh, K.G. Saag, S.L. Bridges, Jr., E.A. Akl, R.R. Bannuru, M.C. Sullivan, E. Vaysbrot, C. McNaughton, M. Osani, R.H. Shmerling, J.R. Curtis, D.E. Furst, D. Parks, A. Kavanaugh, J. O'Dell, C. King, A. Leong, E.L. Matteson, J.T. Schousboe, B. Drevlow, S. Ginsberg, J. Grober, E.W. St Clair, E. Tindall, A.S. Miller, T. McAlindon and R. American College of, 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis, Arthritis Care Res 68 (2016) 1-25.

[64] E.G. Favalli, L. Sinigaglia, A. Becciolini, V. Grosso, R. Gorla, C. Bazzani, F. Atzeni, P.C. Sarzi Puttini, E. Fusaro, R. Pellerito and R. Caporali, Two-year persistence of golimumab as

ACCEPTED MANUSCRIPT

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 21 (2018) 422-430.

[65] M. Elmamoun and V. Chandran, Role of Methotrexate in the Management of Psoriatic Arthritis, Drugs 78 (2018) 611-619.

[66] E.G. Favalli, M. Biggioggero, A. Marchesoni and P.L. Meroni, Survival on treatment with second-line biologic therapy: a cohort study comparing cycling and swap strategies, Rheumatology 53 (2014) 1664-8.

[67] M. Todoerti, E.G. Favalli, F. Iannone, I. Olivieri, M. Benucci, A. Cauli, A. Mathieu, L. Santo, G. Minisola, G. Lapadula, R. Bucci, E. Gremese and R. Caporali, Switch or swap strategy in rheumatoid arthritis patients failing TNF inhibitors? Results of a modified Italian Expert Consensus, Rheumatology 57 (2018) vii42-vii53.

[68] E.G. Favalli, M.G. Raimondo, A. Becciolini, C. Crotti, M. Biggioggero and R. Caporali, The management of first-line biologic therapy failures in rheumatoid arthritis: Current practice and future perspectives, Autoimmunity reviews 16 (2017) 1185-1195.

[69] F. Iannone, G. Ferraccioli, L. Sinigaglia, E.G. Favalli, P. Sarzi-Puttini, F. Atzeni, R. Gorla, C. Bazzani, M. Govoni, I. Farina, E. Gremese, A. Carletto, A. Giollo, M. Galeazzi, R. Foti, L. Bianchino, L. La Grasta and G. Lapadula, Real-world experience of tocilizumab in rheumatoid arthritis: sub-analysis of data from the Italian biologics' register GISEA, Clinical Rheumatol 37 (2018) 315-321.

[70] W. Ye, L.J. Tucker and L.C. Coates, Tapering and Discontinuation of Biologics in Patients with Psoriatic Arthritis with Low Disease Activity, Drugs 78 (2018) 1705-1715.

[71] F. Atzeni, M. Benucci, R. Talotta, I.F. Masala, P. Sarzi-Puttini and M. Govoni, What are the dangers of biological therapy discontinuation or dose reduction strategies when treating rheumatoid arthritis?, Expert Revo Clin Pharmacol 9 (2016) 1403-1411.

[72] A.A. Luong and D.C. Salonen, Imaging of the seronegative spondyloarthropathies, Current rheumatology reports 2 (2000) 288-96.

[73] M.A. D'Agostino and I. Olivieri, Enthesitis, Best practice & research. Clin Rheumatol 20 (2006) 473-86.

[74] A. Rizzo, A. Ferrante, G. Guggino and F. Ciccia, Gut inflammation in spondyloarthritis, Best practice & research. Clin Rheumatol 31 (2017) 863-876.

[75] B. Chen, J. Li, C. He, D. Li, W. Tong, Y. Zou and W. Xu, Role of HLA-B27 in the pathogenesis of ankylosing spondylitis (Review), Mol Med Rep 15 (2017) 1943-1951.

[76] M.M. Luchetti, D. Benfaremo and A. Gabrielli, Biologics in Inflammatory and Immunomediated Arthritis, Current pharmaceutical biotechnology 18 (2017) 989-1007.

[77] M. Benucci, A. Damiani, F. Bandinelli, V. Grossi, M. Infantino, M. Manfredi, F.L. Gobbi, P. Sarzi-Puttini and F. Atzeni, Ankylosing Spondylitis Treatment after First Anti-TNF Drug Failure, IMAJ 20 (2018) 119-122.

[78] L. Gossec, J.S. Smolen, S. Ramiro, M. de Wit, M. Cutolo, M. Dougados, P. Emery, R. Landewe, S. Oliver, D. Aletaha, N. Betteridge, J. Braun, G. Burmester, J.D. Canete, N. Damjanov, O. FitzGerald, E. Haglund, P. Helliwell, T.K. Kvien, R. Lories, T. Luger, M. Maccarone, H. Marzo-Ortega, D. McGonagle, I.B. McInnes, I. Olivieri, K. Pavelka, G. Schett, J. Sieper, F. van den Bosch, D.J. Veale, J. Wollenhaupt, A. Zink and D. van der Heijde, European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update, Ann Rheum Dis 75 (2016) 499-510.

[79] D.J. Veale and U. Fearon, The pathogenesis of psoriatic arthritis, Lancet 391 (2018) 2273-2284.

[80] K. Kruntoradova, J. Klimes, L. Sedova, J. Stolfa, T. Dolezal and A. Petrikova, Work Productivity and Costs Related to Patients with Ankylosing Spondylitis, Rheumatoid Arthritis, and Psoriasis, Value Health Reg Issue 4 (2014) 100-106.

ACCEPTED MANUSCRIPT

[81] C. Evans, Managed care aspects of psoriasis and psoriatic arthritis, Am J Manag Care 22 (2016) s238-43.
[82] P. Kawalec, P. Holko, P. Mocko and A. Pilc, Comparative effectiveness of abatacept, apremilast, secukinumab and ustekinumab treatment of psoriatic arthritis: a systematic review and network meta-analysis, Rheumatol Int 38 (2018) 189-201.
[83] J.A. Singh, G. Guyatt, A. Ogdie, D.D. Gladman, C. Deal, A. Deodhar, M. Dubreuil, J. Dunham, M.E. Husni, S. Kenny, J. Kwan-Morley, J. Lin, P. Marchetta, P.J. Mease, J.F. Merola, J. Miner, C.T. Ritchlin, B. Siaton, B.J. Smith, A.S. Van Voorhees, A.H. Jonsson, A.A. Shah, N. Sullivan, M. Turgunbaev, L.C. Coates, A. Gottlieb, M. Magrey, W.B. Nowell, A.M. Orbai, S.M. Reddy, J.U. Scher, E. Siegel, M. Siegel, J.A. Walsh, A.S. Turner and J. Reston, Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis, Arthritis Care Res 71 (2019) 2-29.
[84] V.P. Bykerk and E.M. Massarotti, The new ACR/EULAR remission criteria: rationale for developing new criteria for remission, Rheumatology 51 Suppl 6 (2012) vi16-20.
[85] D. van der Heijde, J. Sieper, W.P. Maksymowych, M. Dougados, R. Burgos-Vargas, R. Landewe, M. Rudwaleit, J. Braun and S. Assessment of SpondyloArthritis international, 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis, Ann Rheum Dis 70 (2011) 905-8.
[86] J. Braun, T. Pham, J. Sieper, J. Davis, S. van der Linden, M. Dougados, D. van der Heijde and A.W. Group, International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis, Ann Rheum Dis 62 (2003) 817-24.
[87] A. Sepriano, A. Regel, D. van der Heijde, J. Braun, X. Baraliakos, R. Landewe, F. Van den Bosch, L. Falzon and S. Ramiro, 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 3 (2017) e000396.
[88] D. van der Heijde, S. Ramiro, R. Landewe, X. Baraliakos, F. Van den Bosch, A. Sepriano, A. Regel, A. Ciurea, H. Dagfinrud, M. Dougados, F. van Gaalen, P. Geher, I. van der Horst-Bruinsma, R.D. Inman, M. Jongkees, U. Kiltz, T.K. Kvien, P.M. Machado, H. Marzo-Ortega, A. Molto, V. Navarro-Compan, S. Ozgocmen, F.M. Pimentel-Santos, J. Reveille, M. Rudwaleit, J. Sieper, P. Sampaio-Barros, D. Wiek and J. Braun, 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis, Ann Rheum Dis 76 (2017) 978-991.
[89] L.C. Coates, L. Gossec, S. Ramiro, P. Mease, D. van der Heijde, J.S. Smolen, C. Ritchlin and A. Kavanaugh, New GRAPPA and EULAR recommendations for the management of psoriatic arthritis, Rheumatology 56 (2017) 1251-1253.
[90] F. Mahmood, L.C. Coates and P.S. Helliwell, Current concepts and unmet needs in psoriatic arthritis, Clin Rheumatol 37 (2018) 297-305.
[91] F. Atzeni, R. Talotta, I.F. Masala, S. Bongiovanni, L. Boccassini and P. Sarzi-Puttini, Biomarkers in Rheumatoid Arthritis. IMAJ 19 (2017) 512-516.
[92] F. Cantini, L. Niccoli, C. Nannini, E. Cassara, O. Kaloudi, E. Giulio Favalli, A. Becciolini, M. Biggioggero, M. Benucci, F. Li Gobbi, V. Grossi, M. Infantino, F. Meacci, M. Manfredi, S. Guiducci, S. Bellando-Randone, M. Matucci-Cerinic, R. Foti, M. Di Gangi, M. Mosca, C. Tani, F. Palmieri, D. Goletti and T.B.t. Italian board for the, Tailored first-line biologic therapy in patients with rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis, Semin Arthritis Rheum 45 (2016) 519-32.
[93] S. Monti, C. Klersy, R. Gorla, P. Sarzi-Puttini, F. Atzeni, R. Pellerito, E. Fusaro, G. Paolazzi, P.A. Rocchetta, E.G. Favalli, A. Marchesoni and R. Caporali, Factors influencing

ACCEPTED MANUSCRIPT

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 36 (2017) 753-761.

[94] P. van Riel, R. Alten, B. Combe, D. Abdulganieva, P. Bousquet, M. Courtenay, C. Curiale, A. Gomez-Centeno, G. Haugeberg, B. Leeb, K. Puolakka, A. Ravelli, B. Rintelen and P. Sarzi-Puttini, Improving inflammatory arthritis management through tighter monitoring of patients and the use of innovative electronic tools, RMD open 2 (2016) e000302.

[95] M.P. van der Linden, R. Knevel, T.W. Huizinga and A.H. van der Helm-van Mil, 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 63 (2011) 37-42.

[96] R. Fleischmann, S.E. Connolly, M.A. Maldonado and M. Schiff, Brief Report: Estimating Disease Activity Using Multi-Biomarker Disease Activity Scores in Rheumatoid Arthritis Patients Treated With Abatacept or Adalimumab, Arthritis Rheum 68 (2016) 2083-9.

[97] F. Cantini and M. Benucci, Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?, Ann Rheum Dis (2017). Dec 29

[98] A. Marchesoni, I. Olivieri, C. Salvarani, N. Pipitone, S. D'Angelo, A. Mathieu, A. Cauli, L. Punzi, R. Ramonda, R. Scarpa, M. Maccarone and E. Lubrano, 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 35 (2017) 991-1010.

[99] M.F. Rezk and B. Pieper, Treatment Outcomes with Biosimilars: Be Aware of the Nocebo Effect. Rheumatol Ther 4 (2017) 209-218.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

FIGURE LEGENDS

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

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

Figure 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]).

Figure 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]).

Figure 5. Schematic illustration of the 2016 EULAR recommendations for the management of active PsA (modified from Gossec L, et al. Ann Rheum Dis. 2015;74(Suppl2):9; [78]).

Figure 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])

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

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

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

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

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 RA SpA	JAK1 inhibition	Phase 2 Phase 3 Phase 2	Equator Finch 2 Tortuga
Upadacitinib	RA SpA	JAK1 inhibition	Phase 3 Phase 2	Select-next Select Axis 1
Guselkumab	PsA	IL23p19 inhibition	Phase 2	NCT 02319759
Bimekizumab	PsA SpA RA	IL17 A-F inhibition	Phase 3 Phase2 Phase 2	NCT02963506 NCT03355573 NCT02430909
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

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Highlights

- The pharmacological scenario in systemic rheumatic diseases has deeply changed
- Recommendations and guidelines must be followed to choose the correct therapy
- Biosimilars have reduced treatment costs and allowed treating more patients
- Patients clinical conditions and treatment cost must be considered
- The lack of reliable biomarkers is an unmet need in several rheumatic diseases

ACCEPTED MANUSCRIPT

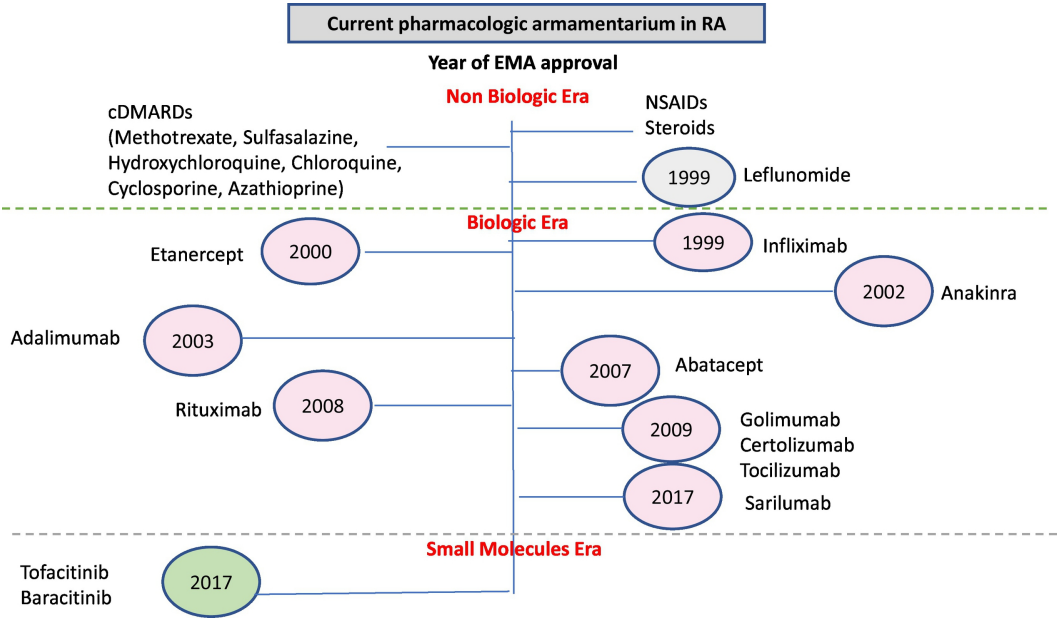

Current pharmacologic armamentarium in RA
Year of EMA approval
Non Biologic Era
cDMARDs
(Methotrexate, Sulfasalazine,
Hydroxychloroquine, Chloroquine,
Cyclosporine, Azathioprine)
NSAIDs
Steroids
1999
Leflunomide
Biologic Era
Etanercept
2000
1999
Infliximab
2002
Anakinra
Adalimumab
2003
2007
Abatacept
Rituximab
2008
2009
Golimumab
Certolizumab
Tocilizumab
2017
Sarilumab
Small Molecules Era
Tofacitinib
Baracitinib
2017

Figure 1

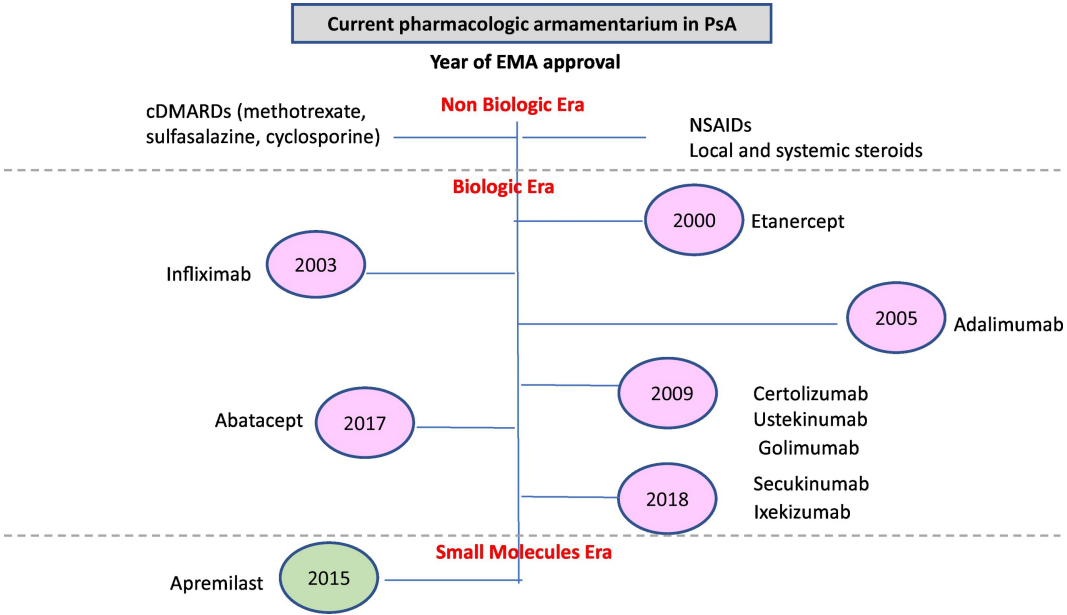
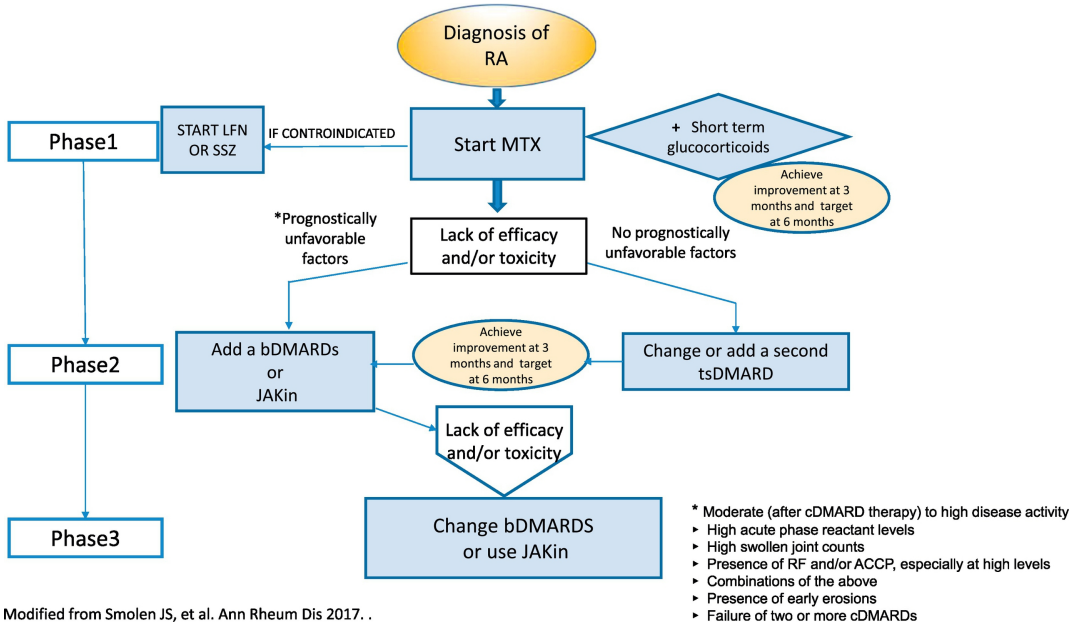

Current pharmacologic armamentarium in PsA
Year of EMA approval
cDMARDs (methotrexate, sulfasalazine, cyclosporine)
Non Biologic Era
NSAIDs
Local and systemic steroids
Biologic Era
2000
Etanercept
Infliximab
2003
2005
Adalimumab
2009
Certolizumab
Ustekinumab
Golimumab
Abatacept
2017
Secukinumab
Ixekizumab
2018
Small Molecules Era
Apremilast
2015

Figure 2



Modified from Smolen JS, et al. Ann Rheum Dis 2017. .

Figure 3

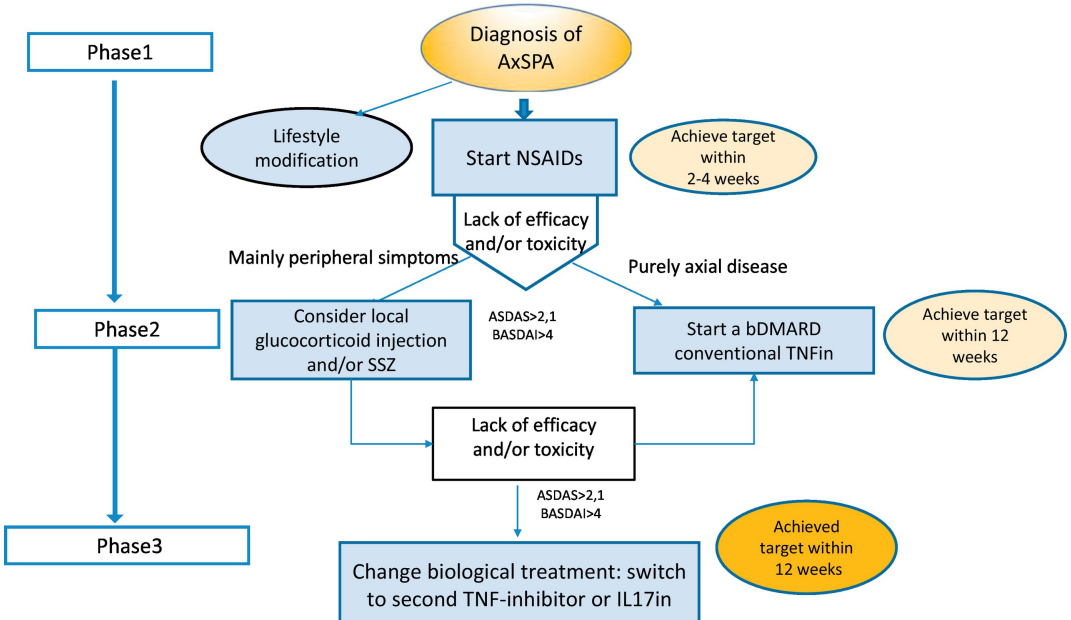

Phase1
Diagnosis of AxSPA
Lifestyle modification
Start NSAIDs
Achieve target within 2-4 weeks
Lack of efficacy and/or toxicity
Mainly peripheral simptoms
Purely axial disease
Phase2
Consider local glucocorticoid injection and/or SSZ
ASDAS>2,1
BASDAI>4
Start a bDMARD conventional TNFin
Achieve target within 12 weeks
Lack of efficacy and/or toxicity
ASDAS>2,1
BASDAI>4
Phase3
Change biological treatment: switch to second TNF-inhibitor or IL17in
Achieved target within 12 weeks

Figure 4

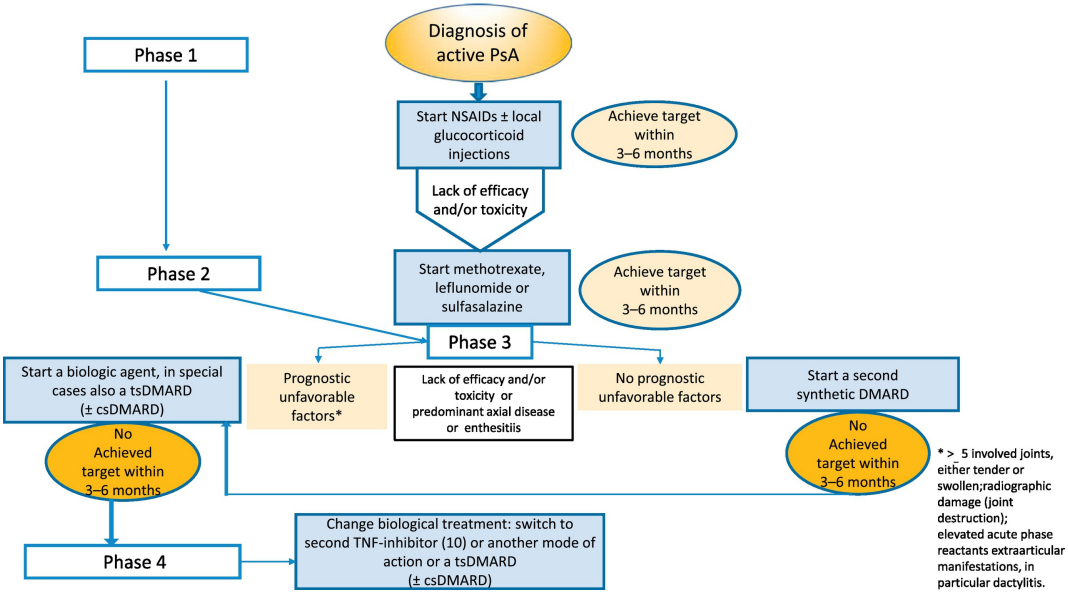

Phase 1
Diagnosis of active PsA
Start NSAIDs ± local glucocorticoid injections
Achieve target within 3–6 months
Lack of efficacy and/or toxicity
Phase 2
Start methotrexate, leflunomide or sulfasalazine
Achieve target within 3–6 months
Phase 3
Start a biologic agent, in special cases also a tsDMARD (± csDMARD)
Prognostic unfavorable factors*
Lack of efficacy and/or toxicity or predominant axial disease or enthesitiis
No prognostic unfavorable factors
Start a second synthetic DMARD
No Achieved target within 3–6 months
No Achieved target within 3–6 months
Phase 4
Change biological treatment: switch to second TNF-inhibitor (10) or another mode of action or a tsDMARD (± csDMARD)
* > 5 involved joints, either tender or swollen;radiographic damage (joint destruction); elevated acute phase reactants extraarticular manifestations, in particular dactylitis.

Figure 5

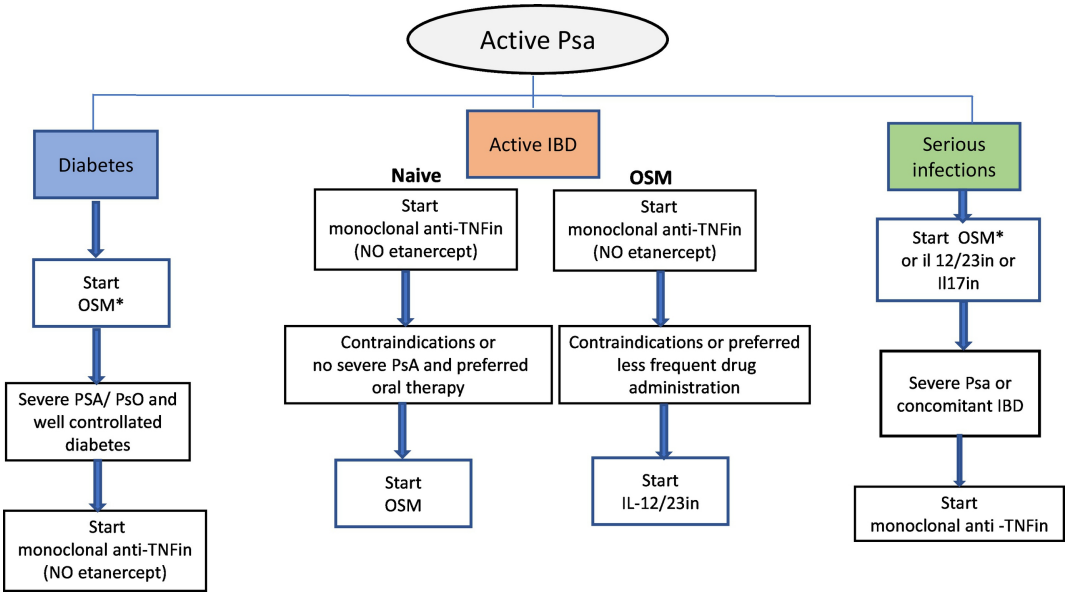

Active Psa
Diabetes
Start
OSM*
Severe PSA/ PsO and
well controllated
diabetes
Start
monoclonal anti-TNFin
(NO etanercept)
Active IBD
Naive
Start
monoclonal anti-TNFin
(NO etanercept)
Contraindications or
no severe PsA and preferred
oral therapy
Start
OSM
OSM
Start
monoclonal anti-TNFin
(NO etanercept)
Contraindications or preferred
less frequent drug
administration
Start
IL-12/23in
Serious
infections
Start OSM*
or il 12/23in or
Il17in
Severe Psa or
concomitant IBD
Start
monoclonal anti -TNFin

Figure 6

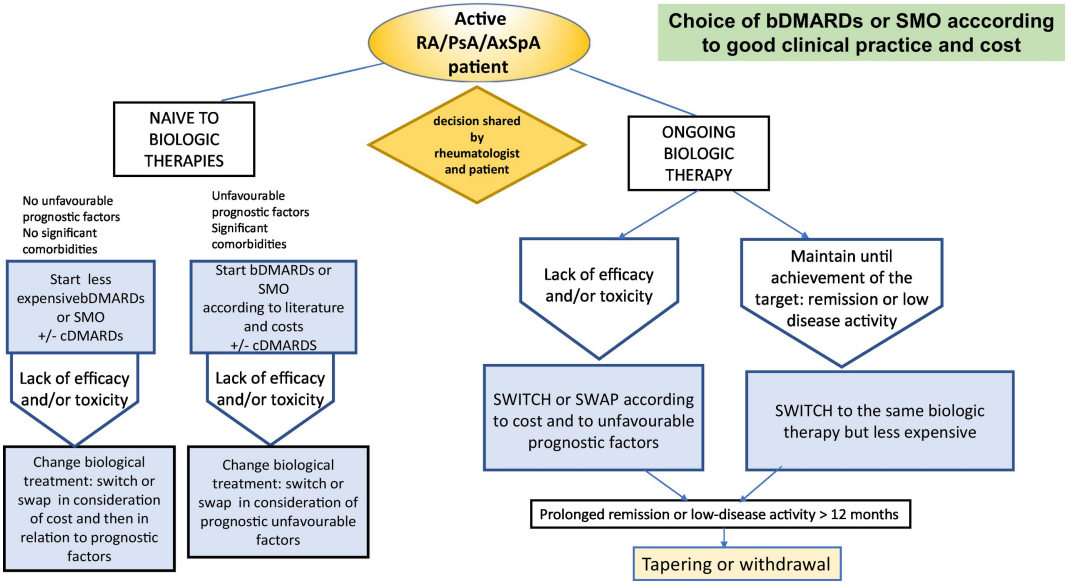

Choice of bDMARDs or SMO acccording to good clinical practice and cost
Active RA/PsA/AxSpA patient
decision shared by rheumatologist and patient
NAIVE TO BIOLOGIC THERAPIES
ONGOING BIOLOGIC THERAPY
No unfavourable prognostic factors
No significant comorbidities
Start less expensivebDMARDs or SMO +/- cDMARDs
Lack of efficacy and/or toxicity
Change biological treatment: switch or swap in consideration of cost and then in relation to prognostic factors
Unfavourable prognostic factors
Significant comorbidities
Start bDMARDs or SMO according to literature and costs +/- cDMARDS
Lack of efficacy and/or toxicity
Change biological treatment: switch or swap in consideration of prognostic unfavourable factors
Lack of efficacy and/or toxicity
SWITCH or SWAP according to cost and to unfavourable prognostic factors
Maintain until achievement of the target: remission or low disease activity
SWITCH to the same biologic therapy but less expensive
Prolonged remission or low-disease activity > 12 months
Tapering or withdrawal

Figure 7