Ther Adv Musculoskel Dis
2020, Vol. 12: 1–12
DOI: 10.1177/1759720X20959971

Immunosuppressive agents for rheumatoid arthritis: a systematic review of clinical trials and their current development stage

Julien Blaess, Julia Walther, Arthur Petitdemange, Jacques-Eric Gottenberg, Jean Sibilia, Laurent Arnaud and Renaud Felten

Abstract

Aims: With the arrival of conventional synthetic (csDMARDs), biological (bDMARDS) and then targeted synthetic (tsDMARDs) disease-modifying anti-rheumatic drugs, the therapeutic arsenal against rheumatoid arthritis (RA) has recently expanded. However, there are still some unmet needs for patients who do not achieve remission and continue to worsen despite treatments. Of note, most randomized controlled trials show that, for methotrexate-inadequate responders, only 20% of patients are ACR70 responders. With our better understanding of RA pathogenesis, finding new treatments is a necessary challenge. The objective of our study was to analyse the whole pipeline of immunosuppressive and immunomodulating drugs evaluated in RA and describe their mechanisms of action and stage of clinical development.

Methods: We conducted a systematic review of all drugs in clinical development in RA, in 17 online registries of clinical trials.

Results: The search yielded 4652 trials, from which we identified 243 molecules. Those molecules belong to csDMARDs ($n = 22$), bDMARDs ($n = 118$), tsDMARDs ($n = 103$). Twenty-four molecules are already marketed in RA in at least one country: eight csDMARDs, 10 bDMARDs and six tsDMARDs. Molecules under current development are mainly bDMARDs ($n = 34$) and tsDMARDs ($n = 33$). Seven of those have reached phase III. A large number of molecules (150/243, 61.7%) have been withdrawn.

Conclusion: Despite the availability of 24 marketed molecules, the development of new targeted molecules is ongoing with a total of 243 molecules in RA. With seven molecules currently reaching phase III, we can expect an increase in the armamentarium in the years to come.

Keywords: bDMARDs, biological, clinical trials, csDMARDs, DMARDs, rheumatoid arthritis, therapeutics, tsDMARDs

Received: 10 June 2020; revised manuscript accepted: 29 August 2020.

Lay summary

- Two hundred and forty-three disease-modifying anti-rheumatic drugs (DMARDs) are assessed in rheumatoid arthritis.
- Sixty-nine molecules are currently in development, mainly biological and targeted synthetic DMARDs.
- Seven molecules are currently reaching phase III, some targeting pathways with no currently marketed molecules.

Correspondence to:
Renaud Felten
Service de Rhumatologie, Hôpitaux Universitaires de Strasbourg, Centre National de Référence des Maladies Autoimmunes et Systémiques Rares, Hôpital de Hautepierre, 1 Avenue Molière BP 83049, Strasbourg, Cedex, 67098, France.
renaud.felten@chru-strasbourg.fr

Julien Blaess
Arthur Petitdemange
Jacques-Eric Gottenberg
Jean Sibilia
Laurent Arnaud
Department of Rheumatology, Hôpitaux Universitaires de Strasbourg, Centre National de Référence des maladies auto-immunes et systémiques rares Est/Sud-Ouest (RESO), Strasbourg, France

Julia Walther
Department of Pharmacy, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

Introduction

Rheumatoid arthritis (RA) is the most frequent chronic inflammatory rheumatic disease, with a prevalence of 0.5–1% of the general population.[1] The therapeutic arsenal of RA has expanded with the arrival of conventional disease-modifying anti-rheumatic drugs (csDMARDs), biological (bDMARDs) and then targeted synthetic (tsDMARDs), leading to an improved prognosis for RA.[2] However, there are still some unmet needs for patients who do not achieve remission and who continue to worsen despite treatment. Of note, only 20–40% of methotrexate-inadequate responders patients are ACR70 responders (ACR [American College of Rheumatology] Response Criteria: ACR70 is ≥ 70% improvement), in most randomized controlled trials.[3] For these patients, finding new treatments is challenging. The better understanding of RA pathogenesis should allow the identification of potential new targets. The objective of our study was to analyse the already marketed DMARDs and the DMARDs under current development, as well as those withdrawn in RA. For those in the pipeline, we sought to describe their mechanisms of action and stage of clinical development. The aim of this systematic review is to provide the reader with an overview of current developments and potentially available therapeutic options in the coming years.

Material and methods

We performed a systematic review of all therapies in clinical development in RA in online registries of clinical trials (Table 1). Two authors (JB and RF) searched 17 national and international databases of clinical trials using the keywords "Rheumatoid arthritis" (search date: 1 June 2019). The study selection process and reasons for exclusion are shown in Figure 1. We excluded from this systematic review non-drug trials, trials not related to RA and duplicates. We also excluded dietary regimen or supplementations, cellular therapies, non-steroidal anti-inflammatory drugs, glucocorticoids or their derivatives and non-immunosuppressive or non-immunomodulating drugs. Finally, we analysed only the immunosuppressive and immunomodulating agents and considered for each molecule the study at the most advanced stage of clinical development, according to the current definitions for phases I, II, III and IV. As far as bDMARDs and their possible biosimilars are concerned, we have considered only the originator molecule. Identified molecules were classified according to Smolen's 2013 DMARDs nomenclature.[4] Biologic drugs, bDMARDs, were defined as a variety of products derived from living organisms by using biotechnology. Targeted therapies, tsDMARDs, were defined as drugs specifically designed to block certain molecules, receptors or pathways involved in the development of autoimmune diseases and that are not bDMARDs. csDMARDs are drugs that inhibit or prevent activity of the immune system in a less targeted way and that are not b- or tsDMARDs. After a first sorting (JB), two authors (RF and JW) made a second double-blind sorting. The final classification was then validated by consensus. The state of development between "marketed", "current development" and "withdrawn" was based on expert feedback, descriptions provided in the registries or additional evidence gathered through the main internet search engines. These data were last updated on 15 April 2020.

Results

The search identified 4652 clinical trials, of which 242 (reporting on a total of 243 molecules) met the inclusion and exclusion criteria. Those molecules belong to csDMARDs ($n = 22$), bDMARDs ($n = 118$), tsDMARDs ($n = 103$).

Many molecules failed and were withdrawn for inefficacy, others for safety concerns and many for lack of perceived commercial competitiveness. We have chosen to focus on and detail only treatments with ongoing development. The withdrawn drugs are listed in the Supplemental Material file S1 online.

csDMARDs

Among the 22 csDMARDs, eight (36.4%) are already marketed in RA, two (9.1%) are in development and 12 (54.5%) have been withdrawn.

Marketed csDMARDs. Common marketed csDMARDs are methotrexate (MTX), sulfasalazine, leflunomide and hydroxychloroquinine.[5]
Bucillamine is a csDMARDs mainly used in Asia (market approval) which has anti-inflammatory properties through NF-KB pathway inhibition.

Ciclosporin, a calcineurin inhibitor, is approved for RA where it can be used in rare cases.

Mizoribine is an inhibitor of inosine monophosphate dehydrogenase mainly used in Japan after renal transplantation and sometimes in RA (market approval).

Table 1. List of international and national databases of clinical trials used for this systematic review.

Database name	Identified trials	URL internet
ClinicalTrials.gov	**210**	https://clinicaltrials.gov
EU Clinical Trials Register (EU-CTR)	**12**	https://www.clinicaltrialsregister.eu
Australian New Zealand Clinical Trials Registry	**9**	https://www.australianclinicaltrials.gov.au
Japan Primary Registries Network	**3**	http://www.umin.ac.jp/ctr/
ISRCTN (International Standard Randomised Controlled Trial Number)	**3**	https://www.isrctn.com
Chinese Clinical Trial Registry	**2**	http://www.chictr.org.cn
Cuban Public Registry of Clinical Trials	**1**	http://registroclinico.sld.cu
Peruvian Clinical Trials Registry	**1**	http://www.ensayosclinicos-repec.ins.gob.pe
Clinical Trials Registry – India	**1**	http://ctri.nic.in
German Clinical Trials Register	0	https://www.drks.de
The Netherlands National Trial Register	0	http://www.trialregister.nl
Brazilian Clinical Trials Registry (ReBec)	0	http://www.ensaiosclinicos.gov.br
Clinical Research Information Service – Republic of Korea	0	https://cris.nih.go.kr
Pan African Clinical Trial Registry	0	http://www.pactr.org
Sri Lanka Clinical Trials Registry	0	http://slctr.lk
Thai Clinical Trials Register	0	http://www.clinicaltrials.in.th
Iranian Registry of Clinical Trials (IRCT)	0	http://www.irct.ir

Tacrolimus, a calcineurin inhibitor, is marketed in Japan and Canada.

csDMARDs in current development. Phase, status and mechanism of action of csDMARDs in current development are summarized in Supplemental Table S2. Two csDMARDs are in current development, one in phase I/II and one in phase II.

Hydroxytriptolide, a traditional Chinese herb (*Trypterigium wilfordii*) compound analogue, has been studied in a completed phase I/II (pending results) and may have an immunomodulating effect on fibroblast-like synoviocytes and their induced inflammatory pathways.[6]

YRA1909, an extract of *Stauntonia hexaphylla*, a herbal supplement which downregulates MMP2 and NF-KB pathways, is currently being assessed in a recruiting phase II trial in Korea.[7]

Withdrawn csDMARDs. The development phase, status and mechanisms of action of the 12 csDMARDs that have been withdrawn are listed in Supplemental Table 1.

bDMARDs

Among the 118 bDMARDs, 10 (8.5%) are already marketed, 34 (28.8%) are in development and 74 (62.7%) have been withdrawn. Currently marketed or in development bDMARDs and their mechanisms of action are summarized in Figure 2. Phase, status and mechanism of action of bDMARDs in current development are summarized in Supplemental Table 2.

Marketed bDMARDs. Among the 118 bDMARDs molecules, 10 (8.5%) are already marketed: rituximab, abatacept, adalimumab, certolizumab-pegol, etanercept, golimumab, infliximab, tocilizumab

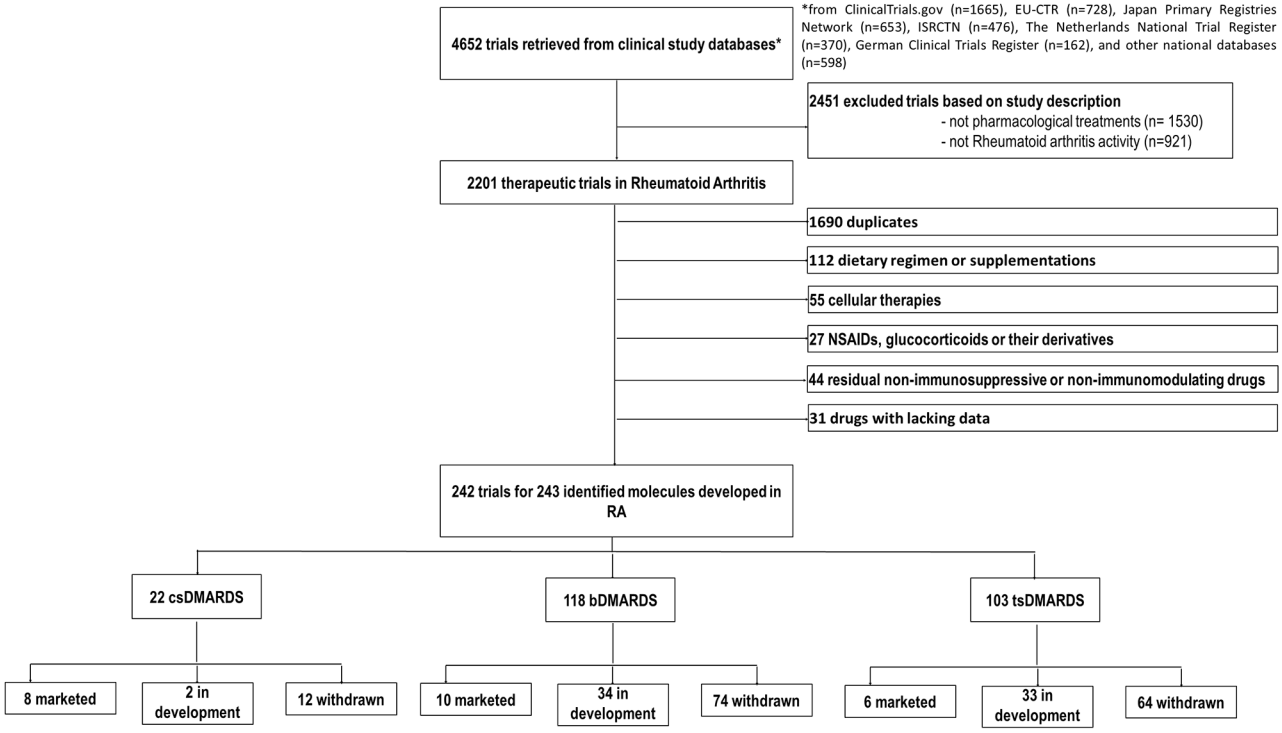

Figure 1. Study flow-chart.
bDMARD, biological disease-modifying anti-rheumatic drug; csDMARD, conventional disease-modifying anti-rheumatic drug; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug.

and sarilumab. Anakinra, a fusion protein targeting interleukin (IL)-1 receptor, is marginally used in RA due to its unfavourable benefit–risk ratio compared with other available treatments.[8]

bDMARDs in current development. Thirty-four bDMARDs are currently in development: seven molecules (20.6%) are in phase I, two (5.9%) in phase I/II, 19 (55.9%) in phase II and six (17.6%) in phase III. They target interleukins or their receptors ($n=14$), other cytokines or chemokines ($n=7$), B cells ($n=4$), T cells or B/T costimulation molecules ($n=4$), integrins or adhesion proteins ($n=2$), interferon receptor ($n=1$) and various or unknown other targets ($n=2$).

Targeting interleukins or their receptors. In addition to tocilizumab and sarilumab, three other molecules targeting IL-6R are studied.

A phase II trial of vobarilizumab, a humanized monoclonal antibody, has been completed showing an ACR50 response rate of 37–49% at week 12.[9]

Levilimab, a fully human monoclonal antibody, is studied in an active but not recruiting phase II trial.

Satralizumab has completed a phase I trial

Three other molecules are targeting directly IL-6.

Olokizumab, a humanized monoclonal antibody, is studied in a recruiting phase III after a previous randomized phase II trial versus placebo.[10]

Clazakizumab completed a phase II trial showing better ACR20 response rates at week 12 compared with MTX alone.[11]

FB704A is a fully human monoclonal antibody studied in a recruiting phase I study.

IL-23 regulates the differentiation of native T-cells into Th17 cells and induces the production of IL-17. IL-17 and IL-23 expression lead to synovial inflammation and promotion of bone destruction by osteoclasts via the NF-KB pathway.[12] Secukinumab, a fully human monoclonal antibody targeting IL-17A, was studied in two phase III trials. It showed no additional benefit versus other therapies in patients with an inadequate response to a first anti TNF-α inhibitor.[13]

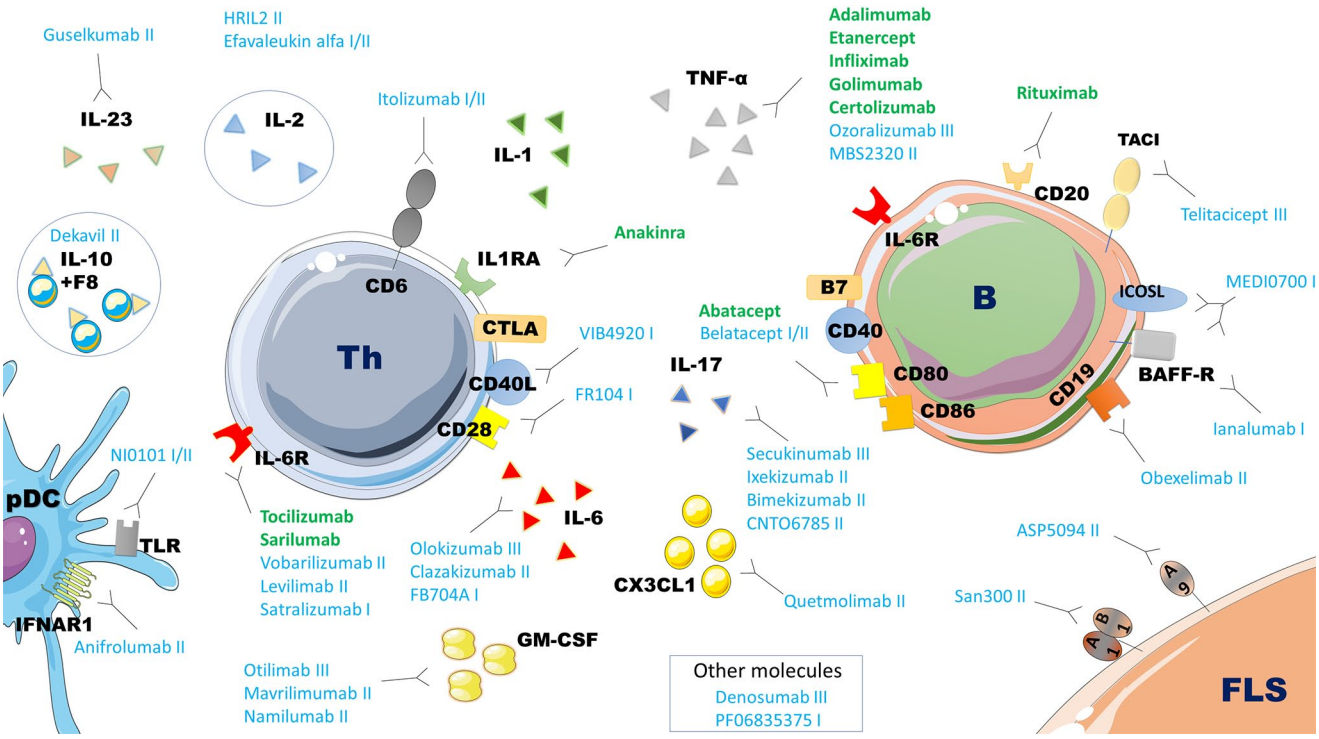

Figure 2. Currently marketed and in development biological disease-modifying anti-rheumatic drugs, their mechanisms of action and development phase (labelled molecules in bold green, molecules in development in blue).
BAFF, B-cell activating factor; CTLA, cytotoxic T-lymphocyte-associated protein; FLS fibroblast-like synoviocyte; GM-CSF, granulocyte-monocyte colony stimulating factor; ICOSL, inducible T cell costimulator ligand; IFNAR, interferon-α/β receptorinterferon-α/β receptor; TACI, transmembrane activator and CAML interactor; TLR, toll-like receptor.

Ixekizumab, a humanized monoclonal antibody targeting IL-17A, has been studied in a completed phase II randomized trial. This trial showed an improvement in RA signs and a good safety profile.[14]

Bimekizumab, a humanized monoclonal antibody with a dual neutralization effect on both IL-17A and IL-17F, was studied in a completed phase II trial, in patients with an inadequate response to certolizumab-pegol. It showed better DAS28 reduction than certolizumab-pegol at week 20.[15]

CNTO6785, a fully human monoclonal antibody targeting IL-17A, was studied in a completed phase II trial. The ACR20 response at week 16 was similar to that of placebo.[16]

Guselkumab is a human monoclonal antibody targeting IL-23p19 licensed in psoriasis. In RA, a phase II trial did not show any improvement in ACR20 response at week 28.[17]

IL-2 is thought to promote regulatory T-cells that have been shown to be dysfunctional in various autoimmune diseases. HRIL2, low dose recombinant human IL-2, has been assessed in a completed single centre (Beijing) phase II trial with positive results (publication is pending).[18]

Efavaleukin alpha, a recombinant IL-2 fusion protein is currently assessed in a phase I/II trial.

IL-10 has an anti-inflammatory effect and downregulates immune responses. Dekavil (F8IL10), a fully human fusion protein composed of the vascular targeting antibody F8 (allowing to target a selective site of inflammation) fused to interleukin-10, is assessed in a recruiting phase II trial.[19]

Targeting other cytokines or chemokines. Ozoralizumab, a humanized monoclonal anti-TNF antibody, is studied in a recruiting phase III study after a positive phase II showing a 84% ACR20 response rate at week 12.[20]

MBS2320 (TNF inhibitor) is evaluated in an active but not yet recruiting phase II study.

In inflamed tissues, granulocyte-monocyte colony stimulating factor (GM-CSF) levels are elevated

and lead to the proliferation and differentiation of myeloid cells. Three anti-GM-CSF antibodies are being tested in RA.

Mavrilimumab, a human monoclonal antibody that inhibits GM-CSF receptor, showed promising results in a phase IIb trial. At week 24, significantly greater ACR50 responses were seen for all mavrilimumab doses (40.5% for 150 mg, 25.9% for 100 mg, and 28.4% for 30 mg versus 12.3% for placebo).

Otilimab, a fully human monoclonal antibody targeting GM-CSF, has been studied in a completed phase II trial. It showed an improvement in DAS28-CRP at week 24 in MTX-IR (inadequate responders) patients. Two phase III trials are now under evaluation against tofacitinib.[21]

Namilumab, a monoclonal antibody that binds GM-CSF, was evaluated in a phase II study. At week 12, a statistically significant difference in DAS28-CRP was seen for namilumab 150 mg versus placebo.[22]

Fractalkine, also called CX3CL1, is a chemokine with a modulating effect on chemotaxis and adhesion. Quetmolimab, a humanized anti-fractalkine monoclonal antibody, has been assessed in a randomized phase II study (not yet published); 400 mg was well tolerated but did not show clear efficacy at week 12 compared with placebo in RA patients with inadequate response to biologics.[23]

PF06835375 is a chemokine receptor antagonist which mechanism is not yet fully understood, currently assessed in a phase I recruiting trial.

B-cells therapies. Telitacicept, a TACI (transmembrane activator and CAML interactor) antibody fusion protein, is assessed in a recruiting phase III study. TACI is a receptor expressed by B-cells and its binding with BAFF (B-cell activating factor) and APRIL (A proliferation-inducing ligand) is involved in B-cells differentiation and proliferation and may contribute to autoimmune diseases through the production of pathogenic immunoglobulins.[24] Two other treatments targeting the same pathway are under evaluation: ianalumab, a human monoclonal antibody (phase I completed in patient with RA: pending results) targeting BAFF-Receptor, and MEDI7000, a bispecific antibody (active phase I but not recruiting) targeting BAFF and ICOS-L (inducible T cell costimulator ligand).

Obexelimab is a bispecific monoclonal antibody targeting CD19 and FcγRIIb which leads to a B-cell inhibition without any depletion.[25] The molecule was studied in a completed phase II, showing positive results with a good safety profile with an improvement in RA outcomes compared with placebo.

Targeting T-cells or B/T costimulation molecules. Itolizumab is a CD6 humanized monoclonal antibody, marketed in cutaneous psoriasis, which downregulates T-cell activation and reduces proinflammatory cytokine secretion. In RA the molecule reached a completed phase II with positive results (at week 12, 50% reached ACR20 response) and a good safety profile.[26]

Belatacept (CTLA4-Ig) is a fusion protein binding CD80 and CD86 on antigen presenting cells with a higher affinity than CD28, leading to an inhibition of the costimulation signal of T-cell activation, as abatacept.[27] It is already labelled in renal transplant rejection and reached a completed phase I/II in RA (pending results). CD40 and CD40L provide a co-stimulating signal for B- and T-cell activation and humoral immune response.

VIB4920, an anti-CD40L present on T-cell surface, completed a phase IB study with positive results (low disease activity or remission in more than 50% of patients).[28] CD28 is the co-receptor for the T-cell receptor.

FR104 is a PEGylated anti-CD28 monoclonal antibody tested in a phase I trial. A phase II study is planned.[29]

Targeting integrins or adhesion proteins. In mouse models, α9 integrin is overexpressed and its inhibition suppressed the development of arthritis.[30] ASP5094 is a recombinant humanized monoclonal targeting α9 integrin subunit, evaluated in a completed phase II trial (pending results).

San300, a α1β1 integrin antagonist, was evaluated in a completed phase II placebo-controlled trial (pending results).

Targeting interferon receptor. Anifrolumab is a fully humanized monoclonal antibody targeting type 1 interferon receptor (IFNAR1) mainly studied in systemic lupus erythematosus. It is currently assessed in a recruiting phase II trial in patients with moderate to severe RA and a high IFN signature.[31]

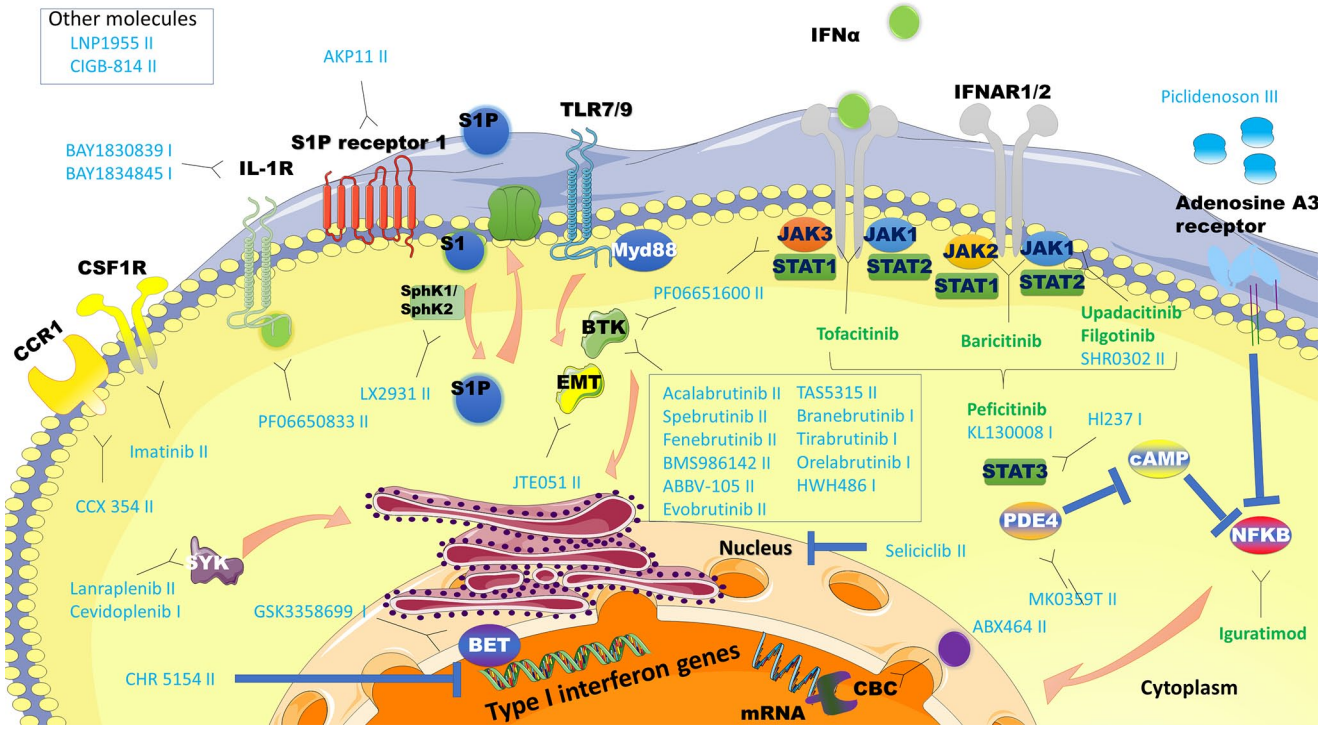

Figure 3. Currently marketed and in development targeted synthetic disease-modifying anti-rheumatic drugs, their mechanisms of action and development phase (labelled molecules in bold green, molecules in development in blue).
BET, Bromodomain and Extra-Terminal domain; BTK, Bruton's Tyrosine Kinase; cAMP, cyclic Adenosine MonoPhosphate; CBC, Cap-Binding Complex; EMT, Epithelial-Mesenchymal Transition; IFNAR, Interferon-α/β Receptor; JAK, Janus Kinase; PDE4, phosphodiesterase 4; STAT, Signal Transducers and Activators of Transcription.

Various or unknown targets. NI0101 is an anti-toll like receptor 4 monoclonal antibody. In a phase II trial in ACPA (Anti-Citrullinated Protein Antibody) positive patients, there was no significant difference in RA clinical outcomes.[32]

RA is characterized by a pathological bone resorption due to osteoclasts. Denosumab is a humanized monoclonal antibody targeting RANKL, an essential mediator of activation, proliferation and survival of osteoclasts, which is already labelled in osteoporosis. It has also been studied in RA in phase III trials, as an add-on therapy, and showed an inhibition of the progression of structural damage.[33]

Withdrawn bDMARDs. The development phase, status and mechanisms of action of the 76 bDMARDs that have been withdrawn are listed in Supplemental Table 1.

tsDMARDs

Among the 103 tsDMARDs molecules, six (5.8%) are already marketed, 33 (32%) are in development and 64 (62.1%) have been withdrawn. Currently marketed and in development tsDMARDs and their mechanisms of action are summarized in Figure 3. Phase, status and mechanism of action of tsDMARDs in current development are summarized in Supplemental Table 2.

Marketed tsDMARDs

Baricitinib, tofacitinib, upadacitinib are oral Janus kinase (JAK) inhibitors which can be used in association with methotrexate.

Peficitinib is a pan-JAK (JAK1, JAK2, JAK3 and Tyk2) inhibitor, approved for RA in Japan since 2019. The Food and Drug Administration and European Medicines Agency did not approve the molecule at this time.[34]

Filgotinib is another selective JAK1 inhibitor which has now a Marketing Authorization Application supported by the European Medicines Agency.

Iguratimod is a small molecule used in Japan and China for treatment of RA acting by inhibition of immunoglobulin production and

suppression of IL-1, IL-6 and TNF-α through the NF-KB pathway.[35]

tsDMARDs in current development

A total of 33 tsDMARDs are in current development: 10 (30.3%) are in phase I, 22 (66.7%) in phase II and one (3.2%) in phase III. tsDMARDs under development target Tec family kinase ($n=12$), cytokines or chemokines ($n=5$), intracellular machinery ($n=4$), JAK ($n=3$), other kinases ($n=2$), sphingosine phosphate pathway ($n=2$), phosphodiesterase ($n=1$) or various targets ($n=4$).

Targeting Tec family kinase. Tec family kinase includes Bruton's tyrosine kinase (BTK), cytoplasmic tyrosine-protein kinase, IL-2-inducible tyrosine kinase (ITK), receptor-like kinase and tyrosine-protein kinase Tec.[36] BTK is a non-receptor Tec family tyrosine kinase involved in B-cells proliferation and activation. Inhibiting BTK allows reducing the number of B-cells and their antibody production like ACPA and rheumatoid factor, which play a central role in RA pathophysiology.[37]

Acalabrutinib is a second generation BTK inhibitor, more selective than those of first generation, marketed in Mantle-cell lymphoma. It was studied in a phase II trial in subjects with RA (pending results). Nine other BTK inhibitors are currently assessed.

Spebrutinib did not reach ACR20 endpoint versus placebo at week 4 but a subgroup analysis suggests potential efficacy in female patients with RA.

Fenebrutinib has shown efficacy in reducing RA activity in patients with an inadequate response to either methotrexate or TNF inhibitors.[38]

For BMS986142, ACR20 and ACR70 rates were not significantly improved at week 12 in a phase II trial.

Evobrutinib, ABBV-105 and TAS5315 are studied in recruiting phase II trials.[39]

Branebrutinib and tirabrutinib have completed phase I trials.

Orelabrutinib and HWH486 are studied in phase I trials.

ITK, also called Emt protein kinase, is involved in T-cell transduction signal after their activation in response to antigen.

JTE051 is an oral ITK inhibitor which completed a phase II trial but showed no statistically significant improvement in ACR20 response rate at week 12.

Targeting cytokines or chemokines. Three interleukin-1 receptor associated kinase 4 (IRAK4) inhibitors are being studied.[40] PF06650833 has completed a positive phase II trial, showing a significant improvement in simplified disease activity index (SDAI) at week 12. BAY1830839 and BAY1834845 are studied in active phase I studies.

Imatinib, a BCR-abl tyrosine kinase inhibitor marketed in chronic myeloid leukaemia, has also colony stimulating factor 1 receptor inhibiting properties, leading to a downregulation of inflammation in the synovial tissue. Imatinib has been assessed in a completed phase II trial (pending results).[41]

CCR1 is a chemokine receptor mostly expressed by leukocytes (neutrophils, T-cells, B-cells and monocytes), involved in leukocytes activation and infiltration. CCX354, a CCR1 inhibitor, has completed a phase II trial which did not reach its primary endpoint (based on ACR20 at week 12).[42]

Targeting the intracellular machinery. Bromodomain and extra-terminal domain (BET) are a family of proteins composed of two tandem bromodomains and an extra-terminal domain which recognize acetylation motifs in histones. BET proteins are involved in gene transcription regulation implicated in cell growth and differentiation through epigenetic interactions between bromodomains and acetylated histones.[43] GSK3358699 is a BET inhibitor assessed in a recruiting phase I trial.

Seliciclib is an oral cyclin-dependent kinase 1, 2, 7 and 9 (CDK) inhibitor assessed in a recruiting phase II study. CDKs are involved in the regulation of the cell cycle, transcription and apoptosis.[44]

ABX464 is studied in an active but not recruiting phase II trial. It is a small oral molecule binding cap binding complex, a promoter of RNA splicing and transcription. It upregulates miR-124, a microRNA which is a modulator involved in immunity and inflammation.[45]

Targeting JAK. Although five JAK inhibitors are already marketed, three more are in current

development. PF06651600, a dual JAK3 and Tec inhibitor, was assessed in a phase II trial with positive results.[46] A phase IIb/III is already planned.

SHR0302 (anti-JAK1) is assessed in an active but not recruiting phase II trial and KL130008 (anti-JAK) in an active phase I.

Targeting other kinases. Syk is a non-receptor tyrosine kinase. Syk plays a role in TNF-α mediated inflammatory cytokines production by fibroblast-like synoviocytes.[47] Lanraplenib, a Syk inhibitor, has completed a phase II trial which did not show improvement on DAS28-CRP at week 12.

Cevidoplenib, another Syk inhibitor, completed a phase I trial, and a phase II trial is planned.

Targeting sphingosine phosphate. Sphingosine 1 phosphate (S1P), overexpressed in RA patients' synovial fluids, is an intracellular second messenger. S1P also plays a role in B-cells' survival, promotes fibroblast-like synoviocytes activation and induces production of inflammatory cytokines and bone resorption.[48] LX2931 is a S1P lyase inhibitor, studied in a phase II trial which did not reach its primary endpoint (based on ACR20 at week 12).

AKP11 is a S1P receptor antagonist studied in a recruiting phase II.

Targeting phosphodiesterase. Phosphodiesterase 4 (PDE4) is an enzyme metabolizing cAMP. The inhibition of PDE4 leads to an increase of cAMP intracellular levels. cAMP is an inhibitor of the NF-KB pathway, decreasing pro-inflammatory cytokine levels and promoting anti-inflammatory cytokines.[49] MK0359 has completed a phase II trial. However, there is no information about the study results and the further development of this molecule.

Other targets. In RA, A3 adenosine receptor is overexpressed.[50] Piclidenoson is a selective agonist of A3 adenosine receptor inducing an anti-inflammatory effect by the inhibition of NF-KB pathway. In two phase II clinical studies, it showed a significant anti-rheumatic effect. A phase III trial is in progress.

LNP1955 is a calcium release-activated channel modulator assessed in a recruiting phase II trial.

Hl237 is a STAT3 transcription factor inhibitor studied in a recruiting phase I trial.

Another therapeutic approach is to induce an immune tolerance with exogenous antigens involved in RA pathophysiology. CIGB-814 is an altered peptide ligand derived from $CD4^+$ T-cells epitope of human heat-shock protein 60 assessed in a phase II trial.[51]

Withdrawn molecules

The development phase, status and mechanisms of action of the 64 tsDMARDs that have been withdrawn are listed in Supplemental Table 1.

Discussion

We performed a systematic review of all molecules in clinical development to analyse the whole pipeline of immunosuppressive and immunomodulating drugs evaluated in RA. A total of 242 therapeutic trials involving 243 molecules have been evaluated in RA. This intense development does not always lead to new treatments since 150 molecules (61.7%) have already been withdrawn. Most of the withdrawn molecules were stopped in early phases, as only 6% (9/150) reached phases II/III or III. Development is shifting towards more targeted molecules as evidenced by the majority of bDMARDs (49.3%) and tsDMARDs (47.8%) under current development compared with only 2.9% csDMARDs.

Sixty-nine molecules are in current development. The most advanced bDMARDs are telitacicept, a TACI antibody fusion protein, ozoralizumab, a TNF-α antibody, olokizumab, an IL-6 antibody, and otilimab, targeting GM-CSF, all reaching phase III trials. Of note, GM-CSF and TACI are pathways with no currently marketed drugs available as opposed to anti-IL6 or anti-TNF therapies.

Concerning tsDMARDs, the five other marketed drugs (except iguratimod) are JAK inhibitors and one-third of molecules in development are BTK inhibitors. The most advanced tsDMARD is piclidenoson, a selective agonist of A3 adenosine receptor, which reached phase III.

Multiple pathways are under clinical investigation and we can expect an increase in our

therapeutic arsenal in the near future. Interleukins are the targets of choice for bDMARDs, with about the half of bDMARDS under development targeting ILs (IL-6, IL-17, IL-23) and their receptors. The targeting of GM-CSF seems interesting since three molecules have shown interesting results in phase II: otilimab, namilumab and mavrilimumab.

This study has some limitations. The development stage of the molecules and the precise mechanism of action are not always made readily available by the manufacturers. The data are also regularly updated and new clinical trials are added, making the information valid only at the time of the study. However, the main strength of this study lies in the systematic review of the clinical trials in 17 international databases and the analysis of all data currently available on each molecule.

Conclusion

Despite the recent arrival of b- and tsDMARDs and the availability of 24 marketed molecules, the exploration of new pathogenic pathways and development of new targeted molecules is ongoing with a total of 243 molecules in RA. With seven molecules currently reaching phase III, some targeting pathways with no currently marketed molecules, we can expect an increase in the armamentarium against RA in the years to come.

Conflict of interest statement

Julien BLAESS, Julia WALTHER and Arthur PETIDEMANGE have no disclosure to declare.

Jacques-Eric GOTTENBERG has received honoraria and research grant from BMS and Pfizer, honoraria from Abbvie, CSL-Behring, Janssen-Cilag, Lilly, Sanofi-Aventis, UCB.

Jean SIBILIA has acted as a consultant for Roche, Chugai, Bristol-Myers Squibb, UCB, GSK, LFB, Actelion, Pfizer, MSD, Novartis, Amgen, Abbvie, Sandoz, Gilead, Lilly, Sanofi Genzyme, Janssen, Mylan.

Laurent ARNAUD has acted as a consultant for Alexion, Amgen, Astra-Zeneca, BMS, GSK, Janssen, LFB, Lilly, Menarini France, Novartis, Pfizer, Roche-Chugaï, UCB.

Renaud FELTEN has acted as a consultant for Abbvie, Biogen, BMS, Lilly, Novartis, MSD, Pfizer, Sanofi, UCB.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Renaud Felten https://orcid.org/0000-0002-4951-4032

Supplemental material

Supplemental material for this article is available online.

References

1. Otón T and Carmona L. The epidemiology of established rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2019; 33: 101477.
2. Smolen JS, Aletaha D and McInnes IB. Rheumatoid arthritis. *Lancet* 2016; 388: 2023-2038.
3. Ma K, Li L, Liu C, *et al.* Efficacy and safety of various anti-rheumatic treatments for patients with rheumatoid arthritis: a network meta-analysis. *Arch Med Sci AMS* 2019; 15: 33–54.
4. Smolen JS, van der Heijde D, Machold KP, *et al.* Proposal for a new nomenclature of disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2014; 73: 3–5.
5. Smolen JS, Landewé RBM, Bijlsma JWJ, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020; 79: 685–699.
6. Guo S, Liu J, Jiang T, *et al.* (5R)-5-Hydroxytriptolide (LLDT-8) induces substantial epigenetic mediated immune response network changes in fibroblast-like synoviocytes from rheumatoid arthritis patients. *Sci Rep* 2019; 9: 11155.
7. Yoo HJ, Kim JY, Kang SE, *et al.* Yra-1909 suppresses production of pro-inflammatory mediators and MMPs through downregulating Akt, p38, JNK and NF-κb activation in rheumatoid arthritis fibroblast-like synoviocytes. *Arthritis Rheumatol* 2017; 69(Suppl. 10): abstract 1412.
8. Mertens M and Singh JA. Anakinra for rheumatoid arthritis: a systematic review. *J Rheumatol* 2009; 36: 1118–1125.
9. Dörner T, Weinblatt M, Beneden KV, *et al.* FRI0239 Results of a phase 2b study of vobarilizumab, an anti-interleukin-6 receptor

nanobody, as monotherapy in patients with moderate to severe rheumatoid arthritis. *Ann Rheum Dis* 2017; 76(Suppl. 2): 575.

10. Takeuchi T, Tanaka Y, Yamanaka H, *et al.* Efficacy and safety of olokizumab in Asian patients with moderate-to-severe rheumatoid arthritis, previously exposed to anti-TNF therapy: results from a randomized phase II trial. *Mod Rheumatol* 2016; 26: 15–23.
11. Weinblatt ME, Mease P, Mysler E, *et al.* The efficacy and safety of subcutaneous clazakizumab in patients with moderate-to-severe rheumatoid arthritis and an inadequate response to methotrexate: results from a multinational, phase IIb, randomized, double-blind, placebo/active-controlled, dose-ranging study. *Arthritis Rheumatol* 2015; 67: 2591–2600.
12. Yuan N, Yu G, Liu D, *et al.* An emerging role of interleukin-23 in rheumatoid arthritis. *Immunopharmacol Immunotoxicol* 2019; 41: 185–191.
13. Blanco FJ, Möricke R, Dokoupilova E, *et al.* Secukinumab in active rheumatoid arthritis: a phase III randomized, double-blind, active comparator- and placebo-controlled study. *Arthritis Rheumatol* 2017; 69: 1144–1153.
14. Genovese MC, Greenwald M, Cho C-S, *et al.* A phase II randomized study of subcutaneous ixekizumab, an anti-interleukin-17 monoclonal antibody, in rheumatoid arthritis patients who were naive to biologic agents or had an inadequate response to tumor necrosis factor inhibitors. *Arthritis Rheumatol* 2014; 66: 1693–16704.
15. Glatt S, Taylor PC, McInnes IB, *et al.* Efficacy and safety of bimekizumab as add-on therapy for rheumatoid arthritis in patients with inadequate response to certolizumab pegol: a proof-of-concept study. *Ann Rheum Dis* 2019; 78: 1033–1040.
16. Mease PJ, Jeka S, Jaller JJ, *et al.* CNTO6785, a fully human antiinterleukin 17 monoclonal antibody, in patients with rheumatoid arthritis with inadequate response to methotrexate: a randomized, placebo-controlled, phase II, dose-ranging study. *J Rheumatol* 2018; 45: 22–31.
17. Smolen JS, Agarwal SK, Ilivanova E, *et al.* A randomised phase II study evaluating the efficacy and safety of subcutaneously administered ustekinumab and guselkumab in patients with active rheumatoid arthritis despite treatment with methotrexate. *Ann Rheum Dis* 2017; 76: 831–839.
18. Low-dose recombinant human IL-2 for the treatment of rheumatoid arthritis - Full Text View - ClinicalTrials.gov [Internet], https://clinicaltrials.gov/ct2/show/NCT02467504 (accessed 8 February 2020).
19. Galeazzi M, Sebastiani G, Voll R, *et al.* FRI0118 Dekavil (F8IL10) – update on the results of clinical trials investigating the immunocytokine in patients with rheumatoid arthritis. *Ann Rheum Dis* 2018; 77(Suppl. 2): 603–604.
20. Fleischmann R, De Bruyn S, Duby C, *et al.* A novel individualized treatment approach in open-label extension study of ozoralizumab (ATN-103) in subjects with rheumatoid arthritis on a background of methotrexate. *ACR Meeting Abstracts* 2012; abstract 1311.
21. Crotti C, Agape E, Becciolini A, *et al.* Targeting granulocyte-monocyte colony-stimulating factor signaling in rheumatoid arthritis: future prospects. *Drugs* 2019; 79: 1741–1755.
22. Taylor PC, Saurigny D, Vencovsky J, *et al.* Efficacy and safety of namilumab, a human monoclonal antibody against granulocyte-macrophage colony-stimulating factor (GM-CSF) ligand in patients with rheumatoid arthritis (RA) with either an inadequate response to background methotrexate therapy or an inadequate response or intolerance to an anti-TNF (tumour necrosis factor) biologic therapy: a randomized, controlled trial. *Arthritis Res Ther* 2019; 21: 101.
23. Tanaka Y, Takeuchi T, Yamanaka H, *et al.* Sat0126 a phase 2 study of E6011, an anti-fractalkine monoclonal antibody, in patients with rheumatoid arthritis inadequately responding to biologics. *Ann Rheum Dis* 2019; 78(Suppl. 2): 1131–1132.
24. Shabgah AG, Shariati-Sarabi Z, Tavakkol-Afshari J, *et al.* The role of BAFF and APRIL in rheumatoid arthritis. *J Cell Physiol* 2019; 234: 17050–17063.
25. Zhao Q. Bispecific antibodies for autoimmune and inflammatory diseases: clinical progress to date. *BioDrugs* 2020; 34: 111–119.
26. Chopra A, Chandrashekara S, Iyer R, *et al.* Itolizumab in combination with methotrexate modulates active rheumatoid arthritis: safety and efficacy from a phase 2, randomized, open-label, parallel-group, dose-ranging study. *Clin Rheumatol* 2016; 35: 1059–1064.
27. Vincenti F, Dritselis A and Kirkpatrick P. Belatacept. *Nat Rev Drug Discov* 2011; 10: 655–656.
28. Karnell JL, Albulescu M, Drabic S, *et al.* A CD40L-targeting protein reduces autoantibodies and improves disease activity in patients with autoimmunity. *Sci Transl Med* 2019; 11: eaar6584.

29. Poirier N, Blancho G, Hiance M, *et al*. First-in-human study in healthy subjects with FR104, a pegylated monoclonal antibody fragment antagonist of CD28. *J Immunol* 2016; 197: 4593–4602.

30. Sugahara S, Hanaoka K and Yamamoto N. Integrin, alpha9 subunit blockade suppresses collagen-induced arthritis with minimal systemic immunomodulation. *Eur J Pharmacol* 2018; 833: 320–327.

31. Felten R, Scher F, Sagez F, *et al*. Spotlight on anifrolumab and its potential for the treatment of moderate-to-severe systemic lupus erythematosus: evidence to date. *Drug Des Devel Ther* 2019; 13: 1535–1543.

32. Monnet E, Choy EH, McInnes I, *et al*. Efficacy and safety of NI-0101, an anti-toll-like receptor 4 monoclonal antibody, in patients with rheumatoid arthritis after inadequate response to methotrexate: a phase II study. *Ann Rheum Dis*. Epub ahead of print 31 December 2019. DOI: 10.1136/annrheumdis-2019-216487.

33. Takeuchi T, Tanaka Y, Soen S, *et al*. Effects of the anti-RANKL antibody denosumab on joint structural damage in patients with rheumatoid arthritis treated with conventional synthetic disease-modifying antirheumatic drugs (DESIRABLE study): a randomised, double-blind, placebo-controlled phase 3 trial. *Ann Rheum Dis* 2019; 78: 899–907.

34. Markham A and Keam SJ. Peficitinib: first global approval. *Drugs* 2019; 79: 887–891.

35. Tanaka K, Yamaguchi T and Hara M. Iguratimod for the treatment of rheumatoid arthritis in Japan. *Expert Rev Clin Immunol* 2015; 11: 565–573.

36. Horwood NJ, Urbaniak AM and Danks L. Tec family kinases in inflammation and disease. *Int Rev Immunol* 2012; 31: 87–103.

37. Whang JA and Chang BY. Bruton's tyrosine kinase inhibitors for the treatment of rheumatoid arthritis. *Drug Discov Today* 2014; 19: 1200–1204.

38. Positive results for fenebrutinib in patients with biologic DMARD refractory RA. *Ann Rheum Dis* 2019; 78: 80–81. (abstract).

39. Goess C, Harris CM, Murdock S, *et al*. ABBV-105, a selective and irreversible inhibitor of Bruton's tyrosine kinase, is efficacious in multiple preclinical models of inflammation. *Mod Rheumatol* 2019; 29: 510–522.

40. McElroy WT. Interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitors: an updated patent review (2016-2018). *Expert Opin Ther Pat* 2019; 29: 243–259.

41. Hu X, Tang J, Hu X, *et al*. Imatinib inhibits CSF1R that stimulates proliferation of rheumatoid arthritis fibroblast-like synoviocytes. *Clin Exp Immunol* 2019; 195: 237–250.

42. Gilliland CT, Salanga CL, Kawamura T, *et al*. The chemokine receptor CCR1 is constitutively active, which leads to G protein-independent, β-arrestin-mediated internalization. *J Biol Chem* 2013; 288: 32194–32210.

43. Taniguchi Y. The bromodomain and extra-terminal domain (BET) family: functional anatomy of BET paralogous proteins. *Int J Mol Sci* 2016; 17: 1849.

44. Khalil HS, Mitev V, Vlaykova T, *et al*. Discovery and development of Seliciclib. How systems biology approaches can lead to better drug performance. *J Biotechnol* 2015; 202: 40–49.

45. Vautrin A, Manchon L, Garcel A, *et al*. Both anti-inflammatory and antiviral properties of novel drug candidate ABX464 are mediated by modulation of RNA splicing. *Sci Rep* 2019; 9: 792.

46. Xu H, Jesson MI, Seneviratne UI, *et al*. PF-06651600, a dual JAK3/TEC family kinase inhibitor. *ACS Chem Biol* 2019; 14: 1235–1242.

47. Deng G-M, Kyttaris VC and Tsokos GC. Targeting syk in autoimmune rheumatic diseases. *Front Immunol* 2016; 7: 78.

48. Lai WQ, Chia FL and Leung BP. Sphingosine kinase and sphingosine-1-phosphate receptors: novel therapeutic targets of rheumatoid arthritis? *Future Med Chem* 2012; 4: 727–733.

49. Sakkas LI, Mavropoulos A and Bogdanos DP. Phosphodiesterase 4 inhibitors in immune-mediated diseases: mode of action, clinical applications, current and future perspectives. *Curr Med Chem* 2017; 24: 3054–3067.

50. Fishman P and Cohen S. The A3 adenosine receptor (A3AR): therapeutic target and predictive biological marker in rheumatoid arthritis. *Clin Rheumatol* 2016; 35: 2359–2362.

51. Corrales O, Hernández L, Prada D, *et al*. CIGB-814, an altered peptide ligand derived from human heat-shock protein 60, decreases anti-cyclic citrullinated peptides antibodies in patients with rheumatoid arthritis. *Clin Rheumatol* 2019; 38: 955–960.