The 2023 pipeline of disease-modifying antirheumatic drugs (DMARDs) in clinical development for spondyloarthritis (including psoriatic arthritis): a systematic review of trials

Agathe Denis,1 Cédric Sztejkowski,1 Laurent Arnaud,1 Guillaume Becker,2 Renaud Felten1,3

ABSTRACT

Objectives The objective of this systematic review was to provide an overview of current developments and potentially available therapeutic options for spondyloarthritis (SpA) in the coming years.

Methods We conducted a systematic review of 17 national and international clinical trial databases for all disease-modifying antirheumatic drugs (DMARDs) for SpA that are already marketed, in clinical development or withdrawn. The search was performed on February 2023 with the keywords “spondyloarthritis”, “ankylosing spondylitis” and “psoriatic arthritis”. For each molecule, we only considered the study at the most advanced stage of clinical development.

Results Concerning axial SpA (axSpA), a total of 44 DMARDs were identified: 6 conventional synthetic DMARDs (csDMARDs), 27 biological DMARDs (bDMARDs) and 11 targeted synthetic DMARDs (tsDMARDs). Among the 18 targeted treatments (b+tsDMARDs) in current development, corresponding trials reached phase I (n=1), II (n=10) and III (n=7). Ten molecules are IL-17 inhibitors, two Janus kinase (JAK) inhibitors and two granulocyte-macrophage colony-stimulating factor inhibitors; four have another mode of action. Concerning psoriatic arthritis (PsA), 44 DMARDs were identified: 5 csDMARDs, 27 bDMARDs and 12 tsDMARDs. Among the 15 molecules in current development, corresponding trials reached phase II (n=8) and III (n=7). Six molecules are JAK inhibitors, six IL-17 inhibitors and one an IL-23 inhibitor; two have another mode of action.

Conclusion This systematic review identified 18 and 15 molecules in clinical development for axSpA and PsA, respectively, which suggests a strengthening of the therapeutic arsenal in the coming years. However, with so many DMARDs but low target diversity, we will need to develop strategies or biomarkers to help clinicians make informed treatment decisions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite the current therapeutic armamentarium, a significant proportion of spondyloarthritis (SpA) patients remain non-responders.

⇒ New treatments are expected to address some of the current unmet needs of these patients.

WHAT THIS STUDY ADDS

⇒ This systematic review identified 63 disease-modifying anti-rheumatic drugs (DMARDs) evaluated for axial SpA (axSpA) and psoriatic arthritis (PsA): 9 conventional synthetic DMARDs, 37 biological DMARDs, 17 targeted synthetic DMARDs.

⇒ Although 17 DMARDs are already marketed, 26 distinct targeted therapies are currently in clinical development, including 18 for axSpA and 15 for PsA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ IL-17 inhibitors represent 56% of the DMARDs in development for axSpA and 40% for PsA.

⇒ Janus kinase inhibitors represent 40% of the DMARDs in development for PsA.

⇒ With so many new DMARDs in development for SpA, but low target diversity, we will need to develop new strategies or biomarkers to help clinicians make informed treatment decisions.

INTRODUCTION

Spondyloarthritis (SpA) represents a wide and heterogeneous spectrum of chronic inflammatory rheumatisms associated with extra-articular manifestations such as psoriasis, inflammatory bowel disease (IBD) and uveitis. Both axial (ankylosing spondylitis and non-radiographic) and peripheral (articular, enthesal, dactylitis) diseases share genetic, immunopathological, clinical and radiological features.

In recent years, the identification of pathogenic mechanisms and the role of several proinflammatory cytokines, including tumour necrosis factor (TNF), interleukin 17...
(IL-17) and IL-23, in the development of SpA have led to the development and routine use of targeted therapies, revolutionising the function and quality of life of patients. In the last two decades, an increasing number of new molecules has been developed. Following the use of TNF inhibitors, new strategies including IL-17 inhibitors, IL-12/23 or IL-23 inhibitors and Janus kinase (JAK) inhibitors have emerged.

Despite this revolution in therapies, there are still several unmet needs. A significant proportion of patients remain non-responders because the proportion of patients achieving partial remission according to Assessment in Ankylosing Spondylitis (ASAS) partial remission response criteria in ankylosing spondylitis ranged from 17% to 22.4% at 24 weeks in randomised controlled trials of TNF inhibitors. Moreover, because of the great variability of clinical phenotypes, the therapeutic strategy is more complex. Indeed, not all molecules are equally efficacious for all manifestations of the disease. For example, IL-17 inhibitors are ineffective in IBD and are therefore not preferred in patients with this extramusculoskeletal manifestation and even contraindicated in patients with active IBD. IL-17 and IL-23 inhibitors have been significantly more effective than TNF inhibitors in treating psoriatic skin disease in large head-to-head phase III trials. Therefore, new molecules and innovative therapeutic strategies need to be discovered to find the most suitable treatment for each patient.

The objective of this systematic review was to identify all disease-modifying antirheumatic drugs (DMARDs) already marketed, in clinical development or withdrawn for the SpA spectrum to provide an overview of potentially available therapeutic options in the coming years.

METHODS
We performed a systematic review of all DMARDs for SpA, including axial SpA (axSpA) and psoriatic arthritis (PsA), that are already marketed, in clinical development or withdrawn from 17 national and international clinical trial databases identified in the WHO registry network, according to the methodology that we previously published.

The search was performed in February 2023 in each database using the keywords “spondyloarthritis”, “ankylosing spondylitis” and “psoriatic arthritis”. First, we excluded trials unrelated to SpA or the evaluation of its activity, non-drug trials and duplicates. A second screening was then performed, and we also excluded dietary supplements and diets, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, non-immunological treatments and cell therapies. Finally, we analysed only the immunosuppressive and immunomodulating agents and considered for each remaining molecule the study at the most advanced stage of clinical development (according to the current definitions for phases I, II, III and IV). Two authors (AD and CS) independently sorted the trials, with arbitration by consensus with two other authors (RF and GB). Then, the molecules were classified according to conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) in the same way, following the 2013 Smolen’s DMARDs nomenclature.

Molecules were classified into the three categories ‘marketed’, ‘in development’ and ‘withdrawn’ based on the information collected in the databases and by cross-referencing internet searches. The molecules still in development in the USA or Europe but already marketed in Asia or Russia were classified as in development.

RESULTS
Our search was performed across 17 national and international clinical trial databases identified by the WHO (table 1). For each keyword, the total number of clinical trials, their sorting and then the classification of the molecules and their stage of development are summarised in figure 1. Overall, the search identified a total of 3574 trials, among which were identified 63 distinct DMARDs. Among the DMARDs, 9 are csDMARDs, 37 bDMARDs and 17 tsDMARDs (figure 1). The development phase, status and mechanism of action of the targeted treatments currently in development are summarised in tables 2–4. The development phase and mechanism of action of the withdrawn DMARDs are in table 5.
Figure 2A summarises the DMARDs that are already marketed or in clinical development (with the most advanced stages of development) according to their indication (axSpA/PsA or both). In figure 2B,C, DMARDs are presented according to their class (cs/b/tsDMARD) and mode of action as well as their stage of development for axSpA (figure 2B) or PsA (figure 2C).

Conventional synthetic DMARDs

Three csDMARDs are currently marketed for PsA: methotrexate, sulfasalazine and leflunomide (figure 2A,C). There is no csDMARD marketed for axSpA (figure 2A,B). According to the most recent European League Against Rheumatism (EULAR) recommendations, patients with purely axial disease should normally not receive csDMARDs, and sulfasalazine may only be considered in patients with peripheral arthritis.3

Iguratimod is a small molecule with anti-inflammatory and immunomodulatory effects, already marketed in China. It is also approved in Japan and China for treating rheumatoid arthritis (RA) because it could inhibit the production of inflammatory cytokines such as IL-1 and TNF, block the IL-17 signalling pathway and inhibit cyclooxygenase.10 Its clinical efficacy was assessed in a phase II monocentric study in China. This study evaluated the efficacy and safety of iguratimod in adults with active axSpA. Patients receiving iguratimod had a significantly lower median NSAID index than those who received a placebo (43.8 (34.9–51.8) vs 68.9 (42.5–86.4), p = 0.025), thus indicating reduced NSAID use. However, the treatment groups did not differ in ASAS response rate or change in disease activity scores, except for improved Spondyloarthritis Research Consortium of Canada score for sacroiliac joints in the iguratimod group.11 Iguratimod is being assessed in a multi-centre recruiting phase III trial for treating axSpA.

No csDMARD is in clinical development for PsA.

Table 2 csDMARDs in current development, phase, status and mechanism of action

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Mechanism of action</th>
<th>Pharmaceutical company/academy</th>
<th>Indications</th>
<th>Current development phase</th>
<th>Current development stage</th>
<th>Clinical trial no</th>
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<tr>
<td>Iguratimod*</td>
<td>Cox2 inhibitor</td>
<td>Qilu Hospital of Shandong University</td>
<td>axSpA</td>
<td>III</td>
<td>Recruiting</td>
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*Marketed in China.

axSpA, axial spondyloarthritis; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; PsA, psoriatic arthritis.
<table>
<thead>
<tr>
<th>Molecule</th>
<th>Molecule code</th>
<th>Mechanism of action</th>
<th>Pharmaceutical company/ academy</th>
<th>Indications (axSpA/PsA)</th>
<th>Current development phase</th>
<th>Current development stage</th>
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<td>Izokibep</td>
<td>ABY 035</td>
<td>IL-17A inhibitor</td>
<td>Inmagene Biopharmaceuticals/ Affibody AB</td>
<td>axSpA/PsA</td>
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<td>Netakimab*</td>
<td>BCD-085</td>
<td>IL-17A inhibitor</td>
<td>Biocad</td>
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<td>Bimekizumab</td>
<td>UCB-4940</td>
<td>IL-17A et F inhibitor</td>
<td>UCB Biopharma SRL</td>
<td>axSpA/PsA</td>
<td>III</td>
<td>Completed</td>
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<td>MoonLake Immunotherapeutics AG</td>
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<td>Brodalumab†</td>
<td>AMG-827</td>
<td>IL 17 receptor inhibitor</td>
<td>Kyowa Kirin/ Bausch Health Americas</td>
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<td>Vunakizumab</td>
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<td>IL-17A inhibitor</td>
<td>Suzhou Suncadia Biopharmaceuticals</td>
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<td>IIb</td>
<td>Recruiting</td>
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<td>IL-17A inhibitor</td>
<td>Genrix (Shanghai) Biopharmaceuticals</td>
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<td>SUNPG 1622</td>
<td>IL-23 p19 inhibitor</td>
<td>Sun Pharmaceutical Industries</td>
<td>PsA</td>
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<td>GM-CSF inhibitor</td>
<td>Izana Bioscience/Iqvia/Innovate UK</td>
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<td>BCD-180</td>
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<td>Anti-TRBV9 monoclonal antibody</td>
<td>Biocad</td>
<td>axSpA</td>
<td>II</td>
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*Marketed for axSpA and PsA in Russia and Belarus.
†Marketed for PsA in Japan.

axSpA, axial spondyloarthritis; DMARDs, disease-modifying antirheumatic drugs; GM-CSF, granulocyte-macrophage colony-stimulating factor; PsA, psoriatic arthritis; TRBV9, T-cell receptor beta variable 9.
<table>
<thead>
<tr>
<th>Molecule</th>
<th>Molecule code</th>
<th>Mechanism of action</th>
<th>Pharmaceutical company/academy</th>
<th>Indications (axSpA/PsA)</th>
<th>Current development phase</th>
<th>Current development stage</th>
<th>Clinical trial no</th>
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<td>III</td>
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<td>Breprocitinib</td>
<td>PF 06700841</td>
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axSpA, axial spondyloarthritis; DMARDs, disease-modifying antirheumatic drugs; JAK, Janus kinase; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis.
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<th>Molecule</th>
<th>Molecule code</th>
<th>Mechanism of action</th>
<th>Pharmaceutical company/ academy</th>
<th>Indications</th>
<th>Development phase</th>
<th>Reason for withdrawal</th>
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<td>Methotrexate</td>
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<td>PsA</td>
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<td>Toxicity: lymphopenia, infection</td>
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<td>AbbVie</td>
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<td>Lack of efficacy</td>
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<td>Janssen Research &amp; Development</td>
<td>axSpA</td>
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<td>AbbVie</td>
<td>axSpA</td>
<td>II</td>
<td>Lack of efficacy</td>
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<td>SUNPG 1622</td>
<td>Sun Pharmaceutical Industries</td>
<td>axSpA</td>
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<td>I</td>
<td>Adverse change in the risk/benefit</td>
<td>NCT03329885</td>
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<td>BI 730357</td>
<td>RORγT antagonist</td>
<td>Boehringer Ingelheim</td>
<td>axSpA PsA</td>
<td>II</td>
<td>Sponsor priorisation</td>
<td>EudraCT 2019-001684-77 NCT04680676</td>
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<tr>
<td>Nilotinib</td>
<td>AMN-107</td>
<td>Bcr-abl tyrosine kinase inhibitor</td>
<td>Academic Medical Center, Division of Clinical Immunology and Rheumatology</td>
<td>axSpA</td>
<td>II</td>
<td>Lack of efficacy</td>
<td>EudraCT 2010-023185-42</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>JAK1, JAK2 and TYK2 inhibitor</td>
<td>Eli Lilly and Company</td>
<td>PsA</td>
<td>III</td>
<td>Sponsor priorisation</td>
<td>EudraCT 2016-004675-52</td>
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<td>ARRY-371797</td>
<td>P38 MAPK inhibitor</td>
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<td>II</td>
<td>No information</td>
<td>NCT00811499</td>
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<td>PDE4 inhibitor</td>
<td>Amgen</td>
<td>axSpA</td>
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<td>Lack of efficacy</td>
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axSpA, axial spondyloarthritis; DMARDs, disease-modifying antirheumatic drugs; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis.
Figure 2  Currently marketed and in-development disease-modifying antirheumatic drugs (DMARDs), their mechanisms of action and development phase. (A) Venn diagram of marketed and in development DMARDs and their development phase in axial spondyloarthritis, psoriatic arthritis or both. (B) Axial spondyloarthritis DMARDs according to their mechanism of action, phases of development and status. (C) Psoriatic arthritis DMARDs according to their mechanism of action, phases of development and status. bDMARDs, biological DMARD; csDMARD, conventional synthetic DMARD; PsA, psoriatic arthritis; tsDMARD, targeted synthetic DMARD.
Details for withdrawn csDMARDs are in table 5. Among the seven withdrawn csDMARDs, five were assessed for axSpA and two for PsA. Among the molecules evaluated for axSpA, methotrexate, hydroxychloroquine and sulfasalazine were withdrawn for lack of efficacy. Thalidomide and olsalazine were assessed in small phase II trials, but no clear information was found to explain their withdrawal. Among the molecules evaluated for PsA, dimethyl fumarate was withdrawn because of sponsor prioritisation and fludarabine because of toxicity concerns (lymphopenia, infection).

**Biological DMARDs**

Marketed bDMARDs or in development as well as their mode of action, phase of development and status are summarised in table 3. Among the 27 bDMARDs assessed for axSpA, 7 molecules are marketed, 13 are in clinical development and 7 have been withdrawn (figure 2A,B). The drugs in current development reached phase I (n=1), phase II (n=8) and phase III (n=4). Among the 27 bDMARDs assessed for PsA, 11 are already marketed, 8 are in current development and 8 have been withdrawn (figure 2A,C). The drugs in development reached phase II (n=4) and phase III (n=4) (table 3).

**TNF inhibitors**

Five TNF inhibitors are marketed for both axSpA and PsA: infliximab, adalimumab, certolizumab pegol, golimumab and etanercept.

The development of remtolumab (ABT-122), a dual-variable domain immunoglobulin (DVD-IgTM) that specifically neutralises both TNF-α and IL-17A has been prematurely terminated (figure 2) because a previous phase II study showed no difference in efficacy between remtolumab and adalimumab over 12 weeks.12-13

**IL-17 inhibitors**

Two IL-17 inhibitors are marketed for both axSpA and PsA: secukinumab, a fully human monoclonal antibody targeting IL-17A, and ixekizumab a humanised monoclonal antibody targeting IL-17A.

Three molecules are at an advanced stage of development. Already marketed for the treatment of plaque psoriasis, PsA and axSpA in Russia and Belarus, netakimab (NTK) is a humanised monoclonal antibody targeting IL-17A. It was assessed in two multicentre phase III trials to evaluate the efficacy of NTK compared with placebo for axSpA (ASTERA) and PsA (PATERA). In ASTERA, ASAS40, response rates were 40.4% with NTK vs 2.6% with placebo at week 16.14 In PATERA, a higher proportion of patients reached American College of Rheumatology (ACR) 20 (82%) and ACR50 (70%) at week 24 with NTK vs placebo (9% and 6%, respectively).15 Approved since 2016 in Japan for treating PsA, brodalumab is a fully human monoclonal antibody that binds to the IL-17 receptor subunit A (IL-17RA) and inhibits the activity of both IL-17A and F. For axSpA, a completed phase III trial showed positive results with ASAS40 response rates of 45.5% at week 16 and 61.6% at week 68.16 Two phase III trials (AMVISION-1 and AMVISION-2) showed that significantly more patients achieved ACR20 at week 16 in both brodalumab treatment groups (45.8% and 47.9% for 140mg and 210mg, respectively).17 Since September 2022, the marketing authorisation for bimekizumab, a monoclonal antibody that selectively neutralises both IL-17A and IL-17F, is under review by the European Medicines Agency (EMA) for axSpA and PsA. Its phase III trial results for axSpA, BE MOBILE 1 and BE MOBILE 2, were presented at EULAR Congress 2022 and showed promising results.18 In BE MOBILE 1, at week 24, the ASAS40 response rates increased to 52.3% for patients initially assigned to bimekizumab and 46.8% for those initially assigned to placebo. In BE MOBILE 2, ASAS40 response rates were 44.8% in the bimekizumab arm vs 22.5% in the placebo arm at week 16.19 Results were also promising in BE OPTIMAL because significantly more patients receiving bimekizumab (44%) reached ACR50 response vs placebo (10%) at week 16.20

Two IL-17A inhibitors are currently in phase II development for axSpA and PsA (figure 2A): vunakizumab, a recombinant humanised monoclonal antibody directly targeting IL-17A assessed in a recruiting phase II study, and izokibep. Izokibep is a small protein molecule that acts as a selective, potent inhibitor of IL-17A, to which it binds with high affinity. It was evaluated in a phase Ib trial in patients with active PsA. The first results were presented at.21 At week 16, the ACR50 response rates were 48% and 52% in the 40mg and 80mg groups, respectively, as compared with 13% in the placebo group. In addition, both treatment groups demonstrated positive response rates in terms of Psoriasis Area and Severity Index 75 (PASI75), a 75% reduction or more in the score, and PASI90, showing efficacy in both the musculoskeletal and cutaneous domains. For axSpA, izokibep has been investigated in a phase II trial prematurely terminated because of the negative impact of COVID-19 restrictions on study recruitment. The trial should be resumed in the next months.

Four other molecules directly targeting IL-17A are being assessed specifically for axSpA (figure 2A). Xelijekimab, a recombinant human IL-17A-neutralising monoclonal antibody, is being evaluated in a phase III trial reported as active but not recruiting. Three other IL-17A inhibitors being assessed in phase II trials are JS005, QX002N and gumokimab.

Sonelokimab is a novel trivalent nanobody targeting IL-17A and IL-17F as well as human serum albumin for plasma half-life extension. Nanobodies are smaller molecules with a potential for better tissue penetration.22 Sonelokimab has been studied in phase I and
II studies showing promising results in psoriasis. It is currently being evaluated in a recruiting phase II trial for PsA.

**IL-12/23 and IL-23 inhibitors**

Three IL-12/23 or IL-23 inhibitors are marketed for PsA. Ustekinumab is a human monoclonal antibody IL-12 and IL-23 antagonist that binds to their p40 subunit. It is marketed for PsA but not for axSpA, given negative results in phase III trials. Guselkumab and risankizumab are IL-23p19 inhibitors recently marketed for PsA. Of note, risankizumab has shown negative results for axSpA, but guselkumab showed positive results in axial manifestations of PsA in a post hoc analysis of 2 trials of PsA. In that analysis, participants with active PsA and imaging-confirmed sacroiliitis who received guselkumab experienced greater improvements in their axial manifestations according to Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) than did placebo-treated participants. These results led to the design of a specific trial to prospectively assess efficacy outcomes of guselkumab in PsA patients with MRI-confirmed axial inflammation, the STAR trial, which is ongoing.

Tildrakizumab is a promising IL-23p19 inhibitor in development for PsA. In a phase IIB study, a significantly greater proportion of patients receiving tildrakizumab achieved ACR20 vs placebo at week 24 (tildrakizumab-treated groups ranging from 71.4% to 79.5% vs 50.6% in the placebo group; all p<0.01). Tildrakizumab also showed improvements in other disease measures, such as skin manifestations but did not significantly affect dactylitis or enthesitis. A phase III trial (INSPIRE 1) is currently recruiting.

Granulocyte-macrophage colony-stimulating factor inhibitors

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a proinflammatory cytokine that can be secreted by T helper 17 cells and induces the differentiation of monocytes, macrophages and dendritic cells into a more inflammatory state. Furthermore, GM-CSF induces osteoclastogenesis via RANK ligand activation, which results in cartilage destruction and bone resorption. High concentrations of GM-CSF have been found in the synovial fluid of axSpA patients, which suggests a role in the pathogenesis of SpA and an interest in targeting this growth factor.

Two human monoclonal antibodies targeting GM-CSF are currently in development for axSpA: gimsilumab, evaluated in a phase I trial, and namilumab, assessed in a completed phase IIa trial (NAMASTE). The study failed to meet its primary endpoint because data showed that 38.9% of namilumab-treated patients achieved ASAS20 at week 12 vs 50% who received placebo. However, its main secondary endpoint was met (improved ASDAS-C reactive protein score at week 6 vs placebo).

**Other targets**

Low-dose recombinant human IL-2 has been evaluated in 11 autoimmune and autoinflammatory diseases, including ankylosing spondylitis and psoriasis but not PsA, in a completed phase II trial (TRANSREG). The results showed an expansion and activation of the T regulatory cell population without the activation of effector T cells. However, no specific results regarding the clinical efficacy of low-dose IL-2 therapy for axSpA have been published.

Abatacept (CTLA4-Ig) is a fusion protein designed to modulate the T-cell co-stimulatory signal mediated through the CD28-CD80/86 pathway. It is marketed and used for treating RA. Given its positive results with a greater ACR20 response vs placebo at week 24 (39.4% vs 22.3%; p<0.001), it has also a Marketing Authorisation Application supported by the EMA, alone or combined with methotrexate for treating PsA although it is much less used in this indication. Abatacept could be a potential treatment option for a select group of patients with PsA, particularly those with active peripheral arthritis without severe cutaneous psoriasis because of only modest improvements as compared with placebo shown in the composite outcome minimal disease activity (MDA), Psoriatic Arthritis Disease Activity Score and Composite Psoriatic Disease Activity Index.

Neihulizumab is an immune checkpoint agonist antibody that regulates T-cell homeostasis. It binds to human CD162 (PSGL-1), thereby preferentially inducing apoptosis in late-stage activated T cells. In a proof-of-concept/efficacy phase Ila trial, 40% of patients with PsA achieved ACR20 response at week 12.

BCD-180 is a monoclonal antibody targeting T-cell receptor beta variable 9 (TRBV9) of B27 T cells. It is currently assessed in a recruiting phase II trial for axSpA.

**Withdrawn bDMARDs**

Details for withdrawn bDMARDs are in table 5. Among the 14 withdrawn bDMARDs, 6 were assessed for axSpA, 7 for PsA and one for both. Among the molecules evaluated for axSpA, 6 showed no significant efficacy: ustekinumab (IL-12/23i), risankizumab and tildrakizumab (both IL-23i), tocilizumab and sarilumab (both IL-6Ri), and abatacept.

Among the molecules evaluated for PsA, remolulmab, a bispecific inhibitor of TNF and IL-17, was withdrawn for lack of efficacy. Alefacept, clazakizumab, GSK3050002 and teplizumab were stopped because of sponsor prioritisation. The development of efalizumab, a CD11a antigen antagonist, was stopped in a phase I trial because of a significant risk of progressive multifocal leukoencephalopathy. We found no information to explain the withdrawal of perakizumab (IL-17Ai).

Rituximab was assessed for both axSPA and PsA, in phase IIb trials, but showed no efficacy.
**Targeted synthetic DMARDs**

tsDMARDs currently in clinical development, as well as their mode of action and stage of development are summarised in table 4. Among the 11 tsDMARDs assessed for axSpA, 2 molecules are marketed, 4 are in clinical development and 5 have been withdrawn (figure 2A,B). The drugs in current development reached phase II (n=2) and phase III (n=2). Among the 12 tsDMARDs assessed for PsA, 3 are already marketed, 7 are in current development and 2 have been withdrawn (figure 2A,C). The drugs in development reached phase II (n=4) and phase III (n=3) (table 4).

**Phosphodiesterase 4 inhibitors**

Apremilast is a selective inhibitor of phosphodiesterase 4 (PDE4) approved for treating PsA and psoriasis. By specifically inhibiting PDE4, the degradation of cAMP is blocked, which regulates inflammation by suppressing or inhibiting the expression of proinflammatory cytokines such as TNF-α, interferon-γ (IFN-γ) and IL-23 and by releasing anti-inflammatory cytokines such as IL-10. It has showed no efficacy in axSpA.17

Mufemilast (Hemay005) is a novel small-molecule inhibitor of PDE4 evaluated in China in a phase III trial for treating psoriasis as well as in an active but not yet recruiting phase II trial for axSpA.

**JAK/signal transducers and activators of transcription inhibitors**

JAK/signal transducers and activators of transcription inhibitors are a group of intracellular kinases involved in the signalling of proinflammatory and anti-inflammatory cytokines. The binding of inflammatory cytokines and chemokines to their receptors initiates downstream signalling pathways. Four JAKs form dimers on the intracellular domains of specific cytokine receptors such as those for IFN-γ, IL-7, IL-12, IL-15, IL-22 and IL-23.18 20 41

Two JAK inhibitors are currently marketed for both PsA and axSpA: upadacitinib, a preferentially JAK1 inhibitor, and tofacitinib, a JAK1/JAK3 inhibitor.

Filgotinib, a preferentially JAK1 inhibitor, had positive results in phase II trials (TORTUGA for axSpA18 and EQUATOR for PsA66). Two phase III trials were developed (SEALION1-1R and SEALION2-NAIVE for axSpA and PENGUIN 1 and PENGUIN 2 for PsA), but both have been withdrawn because of concerns about testicular toxicity. In October 2022, the company Galapagos received positive Committee for Medicinal Products for Human Use opinion after two phase II trials (MANTA and MANTA-Ra2)44 that showed no difference between filgotinib and placebo groups in proportion of patients with 50% or more decline in sperm concentration at week 13. Phase III trials are thus expected to resume soon.

Two phase III trials for axSpA and PsA are currently recruiting to study the efficacy of ivarimatinitib, a selective JAK1 inhibitor also assessed in RA, atopic dermatitis and ulcerative colitis.

Four JAK inhibitors are in development for only PsA: three in phase II and one in phase III (figure 2C).

Deucravacitinib is a novel selective TYK2 inhibitor that selectively inhibits TYK2 via an allosteric mechanism and therefore inhibits cytokines involved in adaptive (IL-12, IL-23) and innate (type I IFNs) immune responses.65 It has recently been approved for treating adults with moderate to severe plaque psoriasis in Europe. Two phase III trials are currently recruiting for PsA (POETYK PsA-1 and POETYK PsA-2) after positive results from its phase II trial. Both doses of deucravacitinib (6 mg once a day and 12 mg once a day) significantly improved ACR20 response vs placebo at week 16 (52.9% and 62.7% vs 31.8%, p=0.0134 and p=0.0004, respectively). Deucravacitinib also conferred significant improvement in secondary endpoints and exploratory efficacy measures.66 NDI-034858 and VTX9598 are two TYK2 inhibitors developed in recruiting phase II trials. Brepocitinib is a selective JAK1 and TYK2 inhibitor. In a phase IIb trial, it showed significant improvement in disease activity. At week 16, significantly higher proportions of patients in the brepocitinib 30 and 60 mg groups versus placebo group achieved an ACR20 response (66.7%, 74.6% and 43.4% with ACR20 response, respectively).17

**Mitogen-activated protein kinase 2 inhibitors**

Mitogen-activated protein kinase (MAPK)-activated protein kinase 2 (MK2) is a kinase downstream of the p38/MAPK complex, a signalling pathway that stimulates transcription and translation of proinflammatory cytokines and chemokines (TNFα, IL-1β, IL-8, IL-6 and IFN-γ).48 49 Because its inhibition is a promising target for blocking the production of inflammatory factors, a phase II trial is currently active but not yet recruiting for CG-99677, an oral selective covalent MK2 inhibitor for axSpA. Zunsemetinib (ATI-450), another orally potent MK2 inhibitor, is being evaluated in a recruiting phase II study for PsA.

**Withdrawn tsDMARDs**

Details for withdrawn tsDMARDs are in table 5. Among the six withdrawn tsDMARDs, four were assessed for axSpA, one for PsA and one for both. Among the molecules evaluated for axSpA, apremilast and nilotinib showed no significant efficacy. The development of BMS-986251, a selective RORγ inverse agonist, was stopped early because of adverse change in the risk/benefit ratio. We found no information to explain the withdrawal of emprumapimod (p38 MAPK inhibitor).

Baricitinib, a selective JAK1 and JAK2 inhibitor, was evaluated for PsA, but its development was stopped because of sponsor prioritisation.

BI 730557 (RORγT antagonist), assessed for both axSpA and PsA in phase II trials, was withdrawn because of sponsor prioritisation.

**DISCUSSION**

We performed a systematic review of trials to analyse the whole pipeline of immunosuppressive and immunomodulating drugs evaluated in the SpA spectrum (axSpA...
and PsA). With the 3 keywords “spondyloarthritis”, “ankylosing spondylitis” and “psoriatic arthritis”, the search identified a total of 3574 trials of 63 DMARDs: 9 csDMARDs, 37 bDMARDs and 17 tsDMARDs.

TNF inhibitors were the first bDMARDs marketed for axSpA and PsA and showing efficacy in reducing spinal inflammation and pain and improving function and quality of life. More recently, research has led to a better understanding of the pathogenesis of SpA, especially with the discovery of the role of the IL-23/IL-17 axis and intracellular pathways and thus has led to the development of new biologics and small molecules. Among these newer molecules, IL-17 inhibitors represent 56% of the DMARDs in development for axSpA and 40% for PsA. Netakimab and brodalumab are leading the way with promising phase III results and marketing authorisation in Asia and Russia. Bimekizumab is currently under review by the EMA for approval in Europe. Izkizibep (a novel bispecific fusion protein) and sonelokimab (an IL-17A, IL-17F and human serum albumin) are opening new ways to target IL-17 with an interesting new way of delivering anti-IL-17 antibodies to tissues. With their small size and very high affinity for IL-17, these two molecules can reach targeted tissues inaccessible to larger antibodies and overcome the limitations of monoclonal antibodies such as poor tissue distribution.

JAK inhibitors also represent a significant proportion of the molecules in clinical development, particularly for PsA, with 40% of the DMARDs in development (11% in axSpA). Among the most advanced molecules are ivarokinitumab, filgotinib and deucravacitinib. Of note, four of the six JAK inhibitors evaluated for PsA are TYK2 inhibitors. Indeed, TYK2 mediates signalling by cytokines such as IL-12 and IL-23 that are involved in the pathogenesis of psoriasis and PsA.

Authorised for PsA, IL-12/IL-23 and IL-23 inhibitors such as ustekinumab, risankizumab and guselkumab show benefits for peripheral musculoskeletal manifestations of PsA such as arthritis, enthesitis and dactylitis. This observation is in contrast to studies showing no significant efficacy of targeting these molecules on signs, symptoms and MRI inflammation in axSpA. One of the explanations is the existence of both IL-23-dependent and IL-23-independent pathways regulating the expression of IL-17, potentially associated with different roles in peripheral and axial skeletal inflammation.

Marketed therapies for SpA are currently targeting only three immune pathways (TNF, IL-17 and IL-23), and novel targets are needed for patients with insufficient response to those treatments. Several new targets are in development, such as GM-CSF, a proinflammatory cytokine that primes TNF and IL-23 responses in myeloid cells from axSpA patients. Namilumab and gimsilumab are two GM-CSF inhibitors being evaluated in phase II and I trials, respectively. The p38/MAPK signalling pathway is also a potential treatment target in SpA. MAPK-MK2 is activated downstream of p38 MAPK and regulates the stability of mRNAs encoding inflammatory cytokines. Zunsemetinib and CC-99677 are oral selective covalent MK2 inhibitors being evaluated in phase II trials for PsA and axSpA, respectively. CC-99677 showed efficacy in a rat model of ankylosing spondylitis and a favourable safety profile in healthy human volunteers in contrast to direct p38 inhibitors. Neihulizumab (immune checkpoint agonist; PSGL-1 ligand) and BCD-180 (monoclonal antibody targeting TRBV9 of B27 T cells) represent original new modes of action that need to be confirmed in the near future.

Some of the molecules in development were first evaluated in other inflammatory diseases, such as the IL-17 inhibitors sonelokimab, nunakizumab and gomukimab for treating psoriasis or ivarokinitumab and zunsemetinib for RA. Other molecules studied in such indications that could reasonably be extended to axSpA and PsA are mirikizumab, an IL-23p19 inhibitor, which has shown positive results in a phase III trial of psoriasis or IBD, brazikumab, another IL-23p19 inhibitor, being evaluated in a phase Iib trial of IBD (EXPEDITION trial).

SpA encompasses a heterogeneous spectrum of conditions, including ankylosing spondylitis, PsA, reactive arthritis and other subtypes. Within this spectrum, there exists a considerable diversity in clinical presentations, disease trajectories and treatment responses. The musculoskeletal domains affected by SpA feature distinct tissue characteristics, which contribute to the complexity of the disease. For instance, SpA can involve the axial skeleton (eg, spine and sacroiliac joints) or peripheral joints (eg, knees, hips and shoulders), and the responsiveness to treatment may vary depending on the specific sites of involvement. Furthermore, extra-articular manifestations represent a prominent feature of SpA, affecting multiple organ systems beyond the joints, such as the skin, eyes, gut and cardiovascular system. The presence of these manifestations introduces additional complexity to the diagnosis and management of SpA. Appreciating the heterogeneity within the SpA spectrum, understanding the tissue-specific variations in treatment response, and acknowledging the intricacies posed by extra-articular manifestations are critical elements in the comprehensive assessment and care of individuals with SpA. By integrating these factors into clinical decision-making, healthcare professionals can tailor treatment strategies to the specific needs of each patient, optimising therapeutic outcomes.

The identification and development of specific molecular targets and intracellular pathways lead to new therapeutic strategies and will probably improve our therapeutic armamentarium for personalised patient treatment. Nevertheless, IL-17 inhibitors represent 56% of the DMARDs in development for axSpA and 40% for PsA, whereas JAK inhibitors represent 40% of the DMARDs in development for PsA. With so many new DMARDs in development for SpA, but low target diversity, we will need to develop new strategies or biomarkers to help clinicians make informed treatment decisions.
The questions that need to be answered are, for example, for a given patient, which treatment should be preferred as the first line of therapy? Which treatment should be preferred after failure of a first line of targeted therapy? Is it better to give an IL-17 inhibitor or IL-23 inhibitor early in the disease and then a TNF inhibitor later on? Can several targeted therapies with different modes of action be combined to achieve greater efficacy? Recently, Simon et al tried to use an alternating treatment regimen that cycled between IL-23 and IL-17 inhibitors in three PsA patients with failure of single inhibition of TNF (adalimumab), IL-23 (guselkumab) and IL-17 (secukinumab). Of note, all three patients reached a MDA state and were continued on this regimen. No infections and no other side effects occurred over the 6 months of treatment. Identifying some biomarkers would also be of great interest to help clinicians make such decisions. Makos et al reviewed many candidate biomarkers that could be used as potential predictors of response to TNF inhibitors in PsA. Unfortunately, to date, none of these markers is used in clinical care because they lack specificity. The authors suggested that a number of diverse candidate biomarkers should be investigated for their predictive qualities. These developments will be crucial for ensuring that patients receive the most effective and appropriate treatments and that we continue to make progress in improving outcomes for people living with SpA.

This study has limitations because it is relied on a time-dependent update of the development pipeline. In addition, we remain dependent on keywords from the description of clinical trials, especially for phase I trials because they evaluate healthy individuals, but also on updates from manufacturers, which can change the status and development stage of clinical trials. However, the marketing process of a molecule is long and one can be aware of the molecules already in phases I and II to have an idea of the potential molecules we will be dealing with in the coming years. The major strength of this study is its overview of all clinical trials included in 17 international databases and the analysis and summary of all data available for each molecule.

Conclusion
This systematic review identified 63 DMARDs evaluated for axSpA and PsA: 9 csDMARDs, 37 bDMARDs and 17 tsDMARDs. Although 17 DMARDs are already marketed, 26 distinct targeted therapies are currently in clinical development, including 18 for axSpA and 15 for PsA.

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