Spondylitis-psoriasis-enthesitis-enterocolitis-dactylitis-uveitis-peripheral synovitis (SPEED-UP) treatment

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Abstract

Axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), psoriasis, inflammatory bowel disease (IBD), and noninfectious uveitis form a distinct group among the immune mediated inflammatory diseases. Thus, many patients suffer from more than one of these disease manifestations. Here, we will use the term spondylitis-psoriasis-enthesitis-enterocolitis-dactylitis-uveitis-peripheral synovitis (SPEED-UP) spectrum disease. The aim is to review the new targeted pharmacological treatment options for all these diseases. All biological or targeted synthetic drugs with U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) approval for any of the diagnoses axSpA, PsA, psoriasis, IBD, or non-infectious uveitis were included. Some of the drugs have documented efficacy in more than one of the diseases, e.g. tumor necrosis factor (TNF) inhibitors. However, other drugs are particularly effective for a specific inflamed tissue and approved in only one or two of the disease entities, e.g. abatacept for peripheral arthritis and vedolizumab for inflammatory bowel disease. This contributes with bedside to bench understanding of the immunology underlying this disease spectrum and provides clinicians with an overview that can assist stratified treatment decisions. We hope that this review will help guide clinicians to speed up treatment of patients with this disease spectrum.

Highlights

- A stratified approach considering all disease entities in patients affected by more than one disease in the spondylitis-psoriasis-enthesitis-enterocolitis-dactylitis-uveitis-peripheral synovitis spectrum can speed up the time to effective treatment
- Clinical trials with targeted drugs give valuable bedside-to-bench knowledge about similarities and differences in the underlying immunological mechanisms of this disease spectrum

Key words

Autoimmunity, immune mediated inflammatory diseases, treatment, disease modifying antirheumatic drugs, immunosuppressive drugs, biologic drugs

1 Introduction

Immune-mediated inflammatory diseases (IMIDs) affect up to 10% of the western population.¹ Among these diseases, axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), psoriasis, inflammatory bowel disease (IBD), and noninfectious uveitis form a distinct group.² Firstly, many patients exhibit overlapping clinical features commensurate with these diagnoses.³⁻⁵ Secondly, numerous newer targeted immunosuppressive drugs have demonstrated efficacy in more than one of the diseases, e.g. tumor necrosis factor (TNF) inhibitors. This implies that there are shared immunological pathways involved. However, some of the immunosuppressive drugs are particularly effective for a specific inflamed tissue and approved in only one or two of the diseases, e.g. abatacept for peripheral arthritis, and vedolizumab for inflammatory bowel disease. Therefore, distinct immunological pathways may also be present in each of the diseases, making the management of patients with more than one of these diseases very challenging. Further adding to the complexity are regulatory requirements and pharmaceutical business decisions resulting in medicines not being currently approved for certain diseases despite evidence of efficacy.

Although an association between these diseases is well known, several challenges currently exist in providing high-quality care for these patients.⁶ Firstly, treatment algorithms from national and international societies often focus on one of the diagnoses. Secondly, management of patients is often organized via a monodisciplinary and siloed health care approach. These shortcomings may lead to inefficient management of the individual patient.

The special disease entities of patients with this group of immune mediated inflammatory diseases are psoriasis in the skin, peripheral and axial arthritis, dactylitis, enthesitis, and immune mediated enterocolitis and uveitis. Some immunological alterations manifest as only one disease entity while other immunological alterations can manifest as two or more disease entities. In this paper, we will use the term spondylitis-psoriasis-enthesitis-enterocolitis-dactylitis-uveitis-peripheral synovitis (SPEED-UP) spectrum disease. The term is used to facility easy reference to the long list of diseases throughout the manuscript. However, the abbreviation also refers to the need to move this field forward at pace given the range of new treatment options available. The focus of this paper is to review the pharmacological treatment options for all these diseases and provide clinicians with an overview that provides stratified treatment decisions.

2 Methods

The diseases axSpA, psoriasis, PsA, IBD, and non-infectious uveitis were included in this review (Table 1). axSpA was separated into radiographic axSpA (r-axSpA; ankylosing spondylitis (AS)) and non-radiographic axSpA (nr-axSpA). The primary disease entity evaluated in psoriasis was chronic plaque psoriasis (henceforth “psoriasis”) with nail psoriasis as a secondary entity. The primary disease entity evaluated in PsA was peripheral synovitis/arthritis with secondary entities being axial arthritis, enthesitis, dactylitis and radiographic progression. IBD was separated into Crohn’s disease (CD) and ulcerative colitis (UC) with fistulating CD as a secondary entity. Non-infectious uveitis here covers HLA-B27 associated uveitis and uveitis in association with HLA-B27 negative arthritis, Bechet’s disease, sarcoidosis as well as idiopathic intermediate, posterior and panuveitis (Table 1).

Any biological or targeted synthetic drug with a U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) approval for any of the diagnoses axSpA, psoriasis, PsA, IBD, or non-infectious uveitis were included. These were the four TNF α specific monoclonal antibodies adalimumab, certolizumab, infliximab, and golimumab, and the TNF-receptor analogue, etanercept; The interleukin 12/23 (IL-12/23) (p40) specific monoclonal antibody ustekinumab, and the three IL-23 (p19) specific monoclonal antibodies guselkumab, risankizumab, and tildrakizumab; The two IL-17A specific monoclonal antibodies secukinumab and ixekizumab; The IL-17 receptor A (IL-17RA) specific monoclonal antibody brodalumab; The cytotoxic-T-lymphocyte-associated protein 4 (CTLA4) analogue (inhibiting cluster of differentiation 80/86 (CD80/86)) abatacept; The α 4 β 7 integrin specific monoclonal antibody vedolizumab; The phosphodiesterase 4 (PDE4) inhibitor apremilast, and finally the Janus kinase (JAK) inhibitor tofacitinib.

Approval documents from FDA and EMA for each included drug were examined for efficacy demonstrated for the primary indications and any secondary disease entities included in this review. If the documents lacked information concerning the secondary disease entities included in this review, the trials in the FDA and EMA approval documents were studied. If a drug was only approved for some of the disease entities included in this review, a literature review on the use of the drug in the other disease entities was conducted using PubMed. The search term was a combination of disease terms and drug terms. A hand-search was done on reference lists of relevant reviews to identify additional studies. Ongoing and previous/terminated trials were found using clinicaltrials.gov. The search included records from database inception to July 13th 2020, which was the date of last search.

Study selection was by screening records for relevance according to title and abstract. Inclusion criteria were randomized controlled trials (RCTs), prospective and retrospective cohort studies and case series concerning biologic and targeted synthetic disease modifying antirheumatic drugs. Prospective and retrospective cohort studies and case series were excluded if any RCT data existed on the disease and drug combination.

The drugs were then divided in five categories (Table 1). 1) EMA or FDA approved. 2) Primary endpoints met in $\geq$ Phase 2 studies. 3) Contraindicated or to be used with caution. 4) Primary endpoint not met in $\geq$ Phase 2 studies. 5) No data or data from trials below phase 2.

3 Results

3.1 TNF α inhibitors

3.1.1 Adalimumab

Adalimumab is approved for all the primary disease entities r-axSpA, nr-axSpA, psoriasis, PsA, CD, UC and non-infectious uveitis by EMA.⁷ Adalimumab is also approved for all the major entities except for nr-axSpA by FDA.⁸ In psoriasis, adalimumab has demonstrated a treatment benefit in specific psoriasis locations including nail and hand and/or foot psoriasis.⁷

3.1.2 Certolizumab Pegol

Certolizumab Pegol is approved by EMA for the treatment of r-axSpA, nr-axSpA, psoriasis and PsA.⁹ Certolizumab Pegol is approved by FDA for r-axSpA, nr-axSpA, psoriasis, PsA, and CD¹⁰, but not UC. Concerning non-infectious uveitis, certolizumab has been studied in a phase III trial with r-axSpA patients showing a decreased rate of non-infectious uveitis flares (3 per 100 patient-years) compared with placebo (10.3 per 100 patient-years)¹¹.

3.1.3 Infliximab

Infliximab is approved for r-axSpA, psoriasis, PsA, CD and UC by EMA¹² and FDA¹³. Infliximab is currently the only anti-TNF α -antibody approved for the treatment of fistulizing CD. Three entities have positive phase three data without approval: There are positive data concerning early r-axSpA (patients with both r-axSpA and nr-axSpA¹⁴), but there are no studies in dedicated nr-axSpA. The drug has been shown to decrease the incidence of non-infectious uveitis in r-axSpA in retrospective trials¹⁵. Lastly, infliximab has demonstrated a treatment benefit in other psoriasis forms/locations including nail psoriasis.¹²

3.1.4 Golimumab

Golimumab is approved for the treatment of r-axSpA, nr-axSpA, PsA and UC by EMA¹⁶ and for the treatment of r-axSpA, PsA and UC by FDA¹⁷. Golimumab has demonstrated an effect on psoriasis in PsA phase 3 trials¹⁸ but is currently not approved for psoriasis by EMA or FDA. In an open label phase 4 study examining the extra-articular manifestations of patients with r-axSpA, golimumab reduced the rate of non-infectious uveitis from 11.1 to 2.2 per 100 patient-years¹⁹.

3.2 TNF α / β inhibitors

3.2.1 Etanercept

Etanercept is approved for the treatment of r-axSpA, nr-axSpA, psoriasis and PsA by EMA²⁰, and for the treatment of r-axSpA, psoriasis, and PsA by FDA²¹. No efficacy on non-infectious uveitis has been indicated in RCTs^{22,23}. Etanercept has been tested in other psoriasis locations including scalp psoriasis²⁴ and open-label trials in nail psoriasis^{25,26} but these secondary disease manifestations have not been specifically approved by the authorities. Etanercept failed to demonstrate efficacy in the treatment of CD²⁷. There are no trials with etanercept in UC.

3.3 IL-12/23 (p40) inhibitors

3.3.1 Ustekinumab

Ustekinumab is approved for the treatment of psoriasis, PsA, CD and UC by EMA²⁸ and FDA²⁹. Additionally, ustekinumab has demonstrated a treatment benefit in nail psoriasis^{28,30}. In three recent placebo-controlled trials, no efficacy of ustekinumab in the treatment of r-axSpA was demonstrated.³¹ Concerning non-infectious uveitis, one non-industry phase 2 clinical study of ustekinumab for active sight-threatening non-infectious uveitis was recently withdrawn (NCT01647152). There are two other non-industry phase II clinical trials studying the efficacy of ustekinumab in non-infectious uveitis still recruiting (NCT02911116, NCT03847272).

3.4 IL-23 (p19) inhibitors

3.4.1 Guselkumab

Guselkumab is approved for the treatment of psoriasis by EMA³² and FDA³³, and was recently approved for PsA treatment by FDA.³³ Guselkumab has demonstrated a treatment benefit in scalp, hand and foot psoriasis and nail psoriasis. There are no current trials of guselkumab concerning r-axSpA, nr-axSpA, non-infectious uveitis or IBD.

3.4.2 Risankizumab

Risankizumab is approved for the treatment of psoriasis by EMA³⁴ and FDA³⁵. Risankizumab failed to meet the primary endpoint of a phase 2 study in biologic naïve patients with r-axSpA³⁶.

Concerning PsA, a recently completed phase two trial proved the drug significantly efficacious on peripheral arthritis compared to placebo, but only numerically more efficacious in dactylitis and enthesitis.³⁷ Furthermore, one trial in PsA is recently completed with data yet to be reported (NCT02719171) and two trials are ongoing (NCT03675308, NCT03671148). Risankizumab has been shown to induce clinical remission in 31% of treated CD patients in a recent phase 2 study³⁸. There are no current studies of risankizumab in non-infectious uveitis or UC.

3.4.3 Tildrakizumab

Tildrakizumab is approved for the treatment of psoriasis by EMA³⁹ and FDA⁴⁰. The drug is currently being investigated in patients with either r-axSpA or nr-axSpA (NCT02980705, NCT03552276) as well as in PsA patients (NCT03552276, NCT02980692). There are no current studies of tildrakizumab in CD, UC or non-infectious uveitis.

3.5 IL-17A inhibitors

3.5.1 Secukinumab

Secukinumab is approved for the treatment of r-axSpA, nr-axSpA, psoriasis and PsA by FDA⁴¹, while EMA approval extends to nail psoriasis as well⁴². A phase 3b trial has reported significant efficacy on axial manifestations of PsA.⁴³ In three phase 3 clinical trials of 118 patients with Bechet's uveitis (SHIELD study), 31 patients with active non-infectious uveitis (INSURE study) and 125 patients with quiescent non-infectious uveitis (ENDURE study), subcutaneous secukinumab did not significantly reduce rates of non-infectious uveitis flares.⁴⁴ Another phase II clinical trial in non-infectious uveitis using intravenous secukinumab dosed at either 30 or 10 mg/kg showed increased response rates compared with the standard 300 mg subcutaneous dose (72.7, 61.5, and 33.3%, respectively)⁴⁵. Secukinumab failed to show any efficacy in the treatment of CD and was even associated with worsening of disease activity in patients with elevated inflammatory parameters⁴⁶.

3.5.2 Ixekizumab

Ixekizumab is approved for the treatment of r-axSpA, nr-axSpA, psoriasis and PsA by FDA⁴⁷, while EMA approval extends to nail psoriasis as well⁴⁸. Ixekizumab has additionally demonstrated a

treatment benefit in specific psoriasis locations including scalp, palmoplantar and genital psoriasis⁴⁹. There are no current trials of ixekizumab in IBD or non-infectious uveitis.

3.6 IL-17RA inhibitors

3.6.1 Brodalumab

Brodalumab is approved for the treatment of psoriasis by EMA⁵⁰ and FDA⁵¹. Brodalumab has demonstrated a treatment benefit in other psoriasis locations including nail and scalp psoriasis⁵⁰. Brodalumab treatment has demonstrated efficacy in Asian r-axSpA and nr-axSpA patients in a phase 3 clinical trial⁵². Concerning PsA, the phase 3 trials AMVISION-1 and -2 showed improvements in peripheral arthritis after 24 weeks.⁵³ A phase 2 study showed efficacy of brodalumab in patients with PsA at week 12 and indicated sustained response through week 52. One treatment arm significantly improved BASDAI scores, indicating some benefit on PsA-related axial arthritis.⁵⁴ A phase 4 study on several psoriatic entities in the Japanese population (NCT04183881) has been completed but not yet reported. However, the drug is currently not approved for PsA or axSpA by EMA or FDA. Brodalumab treatment in patients with active CD was associated with worsening of disease activity and treatment should be avoided in patients with known CD⁵⁵. There are no current trials of brodalumab in UC or non-infectious uveitis.

3.7 CD80/86 inhibitors

3.7.1 Abatacept

Abatacept is approved for PsA by both EMA⁵⁶ and FDA⁵⁷. Only one of the pivotal trials investigated dactylitis and enthesitis. This study failed to reach a significantly higher fraction of patients with complete resolution even though the proportions were numerically higher in the active treatment arms than in the placebo arms⁵⁸. There was no response reported in a prospective open-label pilot r-axSpA study⁵⁹. No significant effect of abatacept was seen on psoriasis in the PsA phase 3 trials^{56,58}. Abatacept has failed to show efficacy in the treatment of CD and UC⁶⁰. There are no current trials of abatacept in non-infectious uveitis.

3.8 $\alpha 4\beta 7$ -integrin inhibitors

3.8.1 Vedolizumab

Vedolizumab is approved for the treatment of CD and UC by both EMA⁶¹ and FDA⁶². Significant efficacy on fistulizing CD has been reported⁶³. There has been several case reports of flare or new occurrence of rheumatic disorders in patients treated with vedolizumab⁶⁴⁻⁶⁶. However, in a recent

cohort of IBD patients treated with vedolizumab no case of induction or flare of arthritis and/or sacroiliitis was reported. Indeed, 6 out of the 14 patients with active SpA (46.2%)—all complaining of peripheral arthropathy—experienced clinical benefit after the initiation of vedolizumab⁶⁷. There are no trials of vedolizumab in SpA, psoriasis, PsA, or non-infectious uveitis.

3.9 PDE4 inhibitors

3.9.1 Apremilast

Apremilast is approved for the treatment of PsA and psoriasis by EMA⁶⁸ and FDA⁶⁹. In addition, apremilast has demonstrated a treatment benefit in scalp and nail psoriasis.⁶⁸ In a phase II study over 12 weeks in 38 patients with symptomatic r-axSpA, apremilast did not meet the primary end point⁷⁰. A larger phase 3 trial including 490 patients have still not been published but preliminary reports suggest a failure of apremilast to meet the primary end point (NCT01583374). A randomized clinical trial evaluating the efficacy of apremilast for the treatment of non-infectious uveitis has been terminated due to lack of efficacy in three subjects enrolled (NCT00889421). There are no trials of apremilast in UC or CD.

3.10 JAK inhibitors

3.10.1 Tofacitinib

Tofacitinib is approved for the treatment of PsA and UC by both EMA⁷¹ and FDA⁷². A phase II dose-ranging trial has shown efficacy of tofacitinib in reducing the signs, symptoms and spinal inflammation of r-axSpA in adults with active disease⁷³. Tofacitinib has demonstrated significant efficacy vs. placebo in patients with psoriasis in two pivotal phase III trials⁷⁴. A further psoriasis? phase 3 trial showed non-inferiority of tofacitinib 10 mg twice daily to etanercept 50 mg twice weekly, whereas tofacitinib 5 mg twice daily did not show non-inferiority to etanercept 50 mg twice weekly⁷⁵. Tofacitinib is currently not approved for psoriasis by EMA or FDA. A phase II clinical trial on non-infectious uveitis is currently registered but not yet recruiting (NCT03580343). Tofacitinib has failed to show efficacy in the treatment of CD⁷⁶.

4 Discussion

The disease entities spondylitis, psoriasis, arthritis, dactylitis, enthesitis, enterocolitis, and non-infectious uveitis are a group of associated IMIDs with shared immunopathology, in which specific targeted immunosuppressive drugs have demonstrated efficacy in more than one of the diseases.

Here, we use the term SPEED-UP (spondylitis-psoriasis-enthesitis-enterocolitis-dactylitis-uveitis-peripheral synovitis) spectrum disease as stated in the introduction. In patients with more than one disease entity the clinical management should therefore, depending on the clinical expression, use an interdisciplinary approach that focus the treatment choice on efficacy in the SPEED-UP-conditions of relevance to the specific patients. These patients experience time consuming multiple clinic visits in different specialties, which neglect some disease manifestations/entities? and the patients are left on their own with the responsibility for coordinating the different treatment approaches^{6,77}. This review emphasizes the need of an interdisciplinary approach concerning patients with SPEED-UP spectrum disease.

As with any IMID, this SPEED-UP spectrum disease is caused by not yet clearly defined alterations in the immune system. Some alterations are associated with one disease entity only while others may cause two or more disease manifestations. Viewing the diseases as caused by common immunological pathways with a variation in clinical phenotype could be an important change in the perception and evaluation of the diseases and lead to more patient centered management. Here, we review the pharmacological treatment options for all entities in the SPEED-UP spectrum disease. Any biological or targeted synthetic drug with FDA or EMA approval for any of the diagnoses axSpA, psoriasis, PsA, IBD, or non-infectious uveitis was included. Hopefully, this will facilitate the clinicians' opportunities to deliver a stratified and tailored treatment (Table 1, Figure 1).

All five TNF inhibitors are approved for one or more entities of SPEED-UP spectrum disease (Figure 1). TNF α is primarily released by macrophages⁷⁸ and plays a crucial role in pro-inflammatory activity.⁷⁹ Adalimumab, infliximab, golimumab, and certolizumab all target both soluble and membrane bound TNF α . Adalimumab, golimumab, and infliximab are all monoclonal antibodies. Certolizumab pegol is a pegylated anti-TNF α fab fragment with prolonged half-life.⁸⁰ Etanercept is a soluble TNF α -receptor analogue and targets both soluble TNF α and lymphotoxin but shows decreased binding capacity to the membrane bound forms. All five TNF α inhibitors are approved for many of the SPEED-UP disease entities. In this way TNF α seems to be a major driver of SPEED-UP spectrum disease. However, studies of the TNF α -receptor analogue etanercept in IBD and non-infectious uveitis did not meet the primary end points^{22,27}. Additionally, numerically lower response rates are reported for etanercept in psoriasis compared to the other TNF α inhibitors⁸¹. This could possibly be due to the less pronounced binding of etanercept to membrane bound TNF α . Monoclonal TNF α inhibitor antibodies binding to membrane bound TNF α has been

reported to induce immune cell apoptosis in IBD in an autocrine fashion, a treatment effect considered of pivotal importance in IBD.⁸²⁻⁸⁵ Therefore, etanercept is not used in patients with significant IBD symptoms as a part of the SPEED-UP disease spectrum. Importantly, the monoclonal TNF α inhibitor antibodies are the only drugs approved for the treatment of non-infectious uveitis. Importantly, TNF α inhibitors are not a one size fits all despite the broad range of effects and the largest number of approvals. As mentioned in the following sections, other drugs are superior to TNF α inhibitors in certain disease manifestations.

Concerning inhibition of the IL-12/23 axis, a single IL-12/23 inhibitor and three IL-23 inhibitors are approved for one or more entities of SPEED-UP spectrum disease (Figure 1). IL-23 is a master regulator of Th17 activity⁸⁶ and maintains Th17 cell expansion and a prolonged upregulation of IL-17A secretion^{87,88}. Ustekinumab is an IL-12/23 (p40) specific monoclonal antibody and is approved for psoriasis, PsA and IBD. Ustekinumab has shown superior efficacy compared with the TNF α / β inhibitor etanercept in head-to-head trials in psoriasis⁸⁹. In contrast, recent trials of ustekinumab in axSpA did not meet the primary endpoints. Also, efficacy on peripheral arthritis appears to be numerically smaller for ustekinumab compared with TNF inhibitors. IL-12/23 inhibition (ustekinumab) has also been approved for the treatment of both CD and UC. Ustekinumab has not been considered the first-line treatment choice in bio-naïve IBD patients since there has been no head to head trials with infliximab. However, in patients not responding to TNF inhibitors, ustekinumab has proved effective. Therefore, ustekinumab treatment may be considered for patients with IBD as the only manifestation and in case of co-occurrence of psoriasis/PsA. The three IL-23 (p19) specific monoclonal antibodies guselkumab, risankizumab, and tildrakizumab are all approved for psoriasis and guselkumab was recently approved for PsA. These drugs have shown superior efficacy compared with some of the TNF inhibitors in head-to-head trials in psoriasis, as guselkumab and risankizumab have achieved significantly higher PASI90 scores than adalimumab^{90,91}, and tildrakizumab has achieved a significantly higher PASI90 score than etanercept.⁹² Meanwhile, IL-23 (p19) specific inhibition failed in axSpA trials.³⁶ Therefore, IL-23 inhibition might not be first choice in patients with axSpA. The trials of the IL-23 (p19) specific monoclonal antibodies in PsA are ongoing and will show whether the effect on peripheral arthritis is numerically closer to ustekinumab or TNF inhibition. The lack of effect of IL-23 inhibition in axSpA is surprising considering the role of IL-23 in the IL-23-Th17 axis. However, IL-23 has other functions and IL-17A is secreted by many other cell types than Th17 cells. Collectively, IL-12/23

and IL-23 inhibition is efficacious in many SPEED-UP spectrum entities but will likely not be first choice in patients with axSpA involvement⁹³.

Three inhibitors of IL-17 cytokines and receptors are approved for one or more entities of SPEED-UP spectrum disease (Figure 1). The IL-23-Th17 axis is a majorly influencing factor in the pathogenesis of SPEED-UP spectrum disease⁹⁴. IL-17A release results in inflammation, matrix destruction, cartilaginous damage and bone erosion.⁹⁵ Secukinumab and ixekizumab are both monoclonal antibodies targeting IL-17A.^{95,96} These drugs are approved for axSpA, psoriasis and PsA. Brodalumab is a monoclonal antibody directed against the IL-17RA.⁹⁷ This drug has so far only been approved for psoriasis. IL-17 inhibition has also shown superiority compared with TNF α inhibition in head-to-head trials in psoriasis.⁹⁸⁻¹⁰⁰ Blocking IL-17A signaling both at the cytokine level and at the receptor level has been shown to be superior to ustekinumab in clinical trials in psoriasis.^{98,101} Head-to-head psoriasis trials have shown superiority of two IL-23(p19) inhibitors compared with secukinumab^{102,103}, whereas ixekizumab, has shown superiority compared with guselkumab in short-term psoriasis endpoints¹⁰⁴. This could be because of differences between the IL-17A inhibitors but could also be the result of differences in clinical trial design. Importantly, both ixekizumab and secukinumab were not inferior compared with adalimumab in head-to-head trials in PsA^{105,106}. Taken together, IL-17A seems to be more important compared with TNF α in skin disease and more important compared with IL-23 in axial disease in SPEED-UP spectrum disease. In contrast, a trial of IL-17A inhibition with secukinumab in CD patients showed no effect of the drug and higher rates of disease-worsening, leading to early termination of the trial.⁴⁶ Indeed, IBD related adverse events have been described in trials of IL-17 inhibition in SpA, psoriasis and PsA¹⁰⁷. Therefore, IL-17 inhibition is not recommended in patients with active IBD as one of the disease manifestations of SPEED-UP spectrum disease.

The CTLA4 analogue (inhibiting CD80/86) abatacept is approved for PsA. T-cell activation requires binding of the co-stimulatory receptor CD28 to CD80/86 on an antigen presenting cell. Abatacept is therefore considered to function via suppression of T cell responses.¹⁰⁸ Interestingly, inhibition of CTLA4 is being used in oncology to activate CD8 positive T cells against tumor cells. This treatment may in some cases elicit immune mediated adverse events resembling psoriasis skin disease, seronegative arthritis and ulcerative colitis¹⁰⁹. However, trials with abatacept failed to meet the primary end point in both SpA, psoriasis, and IBD. So, abatacept should only be used in patients with peripheral arthritis.

The $\alpha 4\beta 7$ integrin specific monoclonal antibody vedolizumab is approved for the treatment of IBD. The integrin $\alpha 4\beta 7$ is expressed by a subset of lymphocytes and binds MAdCAM-1 on vascular endothelial cells in the gastrointestinal tract. Vedolizumab is believed to be rather specific in preventing migration of gut homing lymphocytes to the lamina propria. The drug has therefore not been studied in other entities of SPEED-UP spectrum disease. Therefore, vedolizumab should only be used in patients with IBD as the dominating disease entity.

The PDE4 inhibitor apremilast is approved for the treatment of psoriasis and PsA. Apremilast is an orally administered, small-molecule drug inhibiting PDE4. PDE4 inhibition mediates a continuously high intracellular cAMP-concentration, thereby inhibiting the production of proinflammatory cytokines (Figure 1).¹¹⁰ The main cytokine inhibited by apremilast treatment of synovial fluid mononuclear cells was the IL-12/23 p40 subunit.¹¹¹ Apremilast has shown efficacy primarily in psoriasis. However, PASI75 improvement appears to be numerically smaller with apremilast compared with monoclonal TNF α inhibitor antibodies and biological drugs targeting IL-12/23, IL-23, and IL-17. Apremilast is also approved for peripheral PsA. However, the effect is limited on ACR70 responses and radiographic data is still lacking. Thus, apremilast can be used in patients with psoriasis and perhaps mild PsA⁹³.

The JAK inhibitor tofacitinib is approved in PsA and IBD (UC only). However, many studies with different JAK inhibitors are ongoing. The intracellular JAK pathway mediates expression of key pro-inflammatory cytokines and growth factors (Figure 1).¹¹² Tofacitinib is a JAK1/3 inhibitor with a limited effect on JAK 2. Some of the cytokines inhibited by tofacitinib are also the targets of other drugs approved for the treatment of SPEED-UP spectrum disease including IL-12 and IL-23. Several other cytokines could be implicated such as IL-2, IL-7, and the IL-20 cytokine family¹¹³. In UC, tofacitinib often improves symptoms after a few days of treatment. The tofacitinib 10 mg twice daily dose regimen is usually used for three months and subsequently reduced to 5mg twice daily. Importantly, JAK inhibition is still not approved for psoriasis. This is mainly because the tofacitinib 10 mg twice daily dose has been linked to increased risk of side effects and because the tofacitinib 5 mg twice daily dose was inferior compared with etanercept. However, the tyrosine kinase 2 (TYK2) pathway, another member of the JAK family, seems to be important in psoriasis pathophysiology and selective TYK2 inhibition has shown promising results in a phase 2 trial of psoriasis¹¹⁴. The cytokines mediated by the TYK2 signaling pathway include IL-12, IL-23 and the IL-20 cytokine family and could therefore be more specific

for psoriasis with a better safety profile. Taken together, tofacitinib is still primarily recommended in patients dominated by peripheral arthritis or ulcerative colitis.

There are several limitations in this review. First, the adverse event profiles and the long-term follow-up data on the different drugs were not included. This information will be important for the choice of treatment in many patients. Second, the route of administration and drug prices were not considered. These might be very important factors in many health care systems. Third, non-steroidal anti-inflammatory drugs and conventional synthetic immunosuppressive drugs such as methotrexate, azathioprine, dimethyl fumarate, and leflunomide were not taken into consideration even though combinations with these drugs are indicated in many patients with SPEED-UP spectrum disease. Further, effect sizes of the drugs have not been systematically reported. Therefore, this review cannot be used to position the different products. Finally, we did not discuss switching between drugs. Prior failed medications need to be considered in the treatment decision.

Taken together, we have reviewed the pharmacological treatment options for all entities and manifestations of what we here term in SPEED-UP spectrum disease. Any biological or targeted synthetic drug with FDA or EMA approval for any of the diagnoses axSpA, psoriasis, PsA, IBD, or non-infectious uveitis was included. We hope that this review will help guide clinicians to speed up treatment of patients with these diseases.

5 Authors' contributions

MB, AD, KFJ, and TWK performed the literature search and wrote the result sections. MBK and TWK made the first draft of the manuscript. All authors were involved in analysis and interpretation of data and critically revising the manuscript for intellectual content. All authors read and approved the final version.

6 Ethics approval and consent to participate

Not applicable.

7 Disclosures/conflict of interest:

TWK has engaged in educational activities receiving speaking fees from Pfizer, Bristol-Myers Squibb, Eli Lilly, Novartis, and UCB and has been consultant and advisor for Bristol-Myers Squibb

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AGL advisory board for AbbVie, Pfizer, MSD, Novartis, Lilly and speaker and educational sessions for MSD, Novartis, Pfizer and UCB.

LI has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by: AbbVie, Almirall, Amgen, Astra Zeneca, BMS, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Janssen Cilag, Kyowa, Leo Pharma, MSD, Novartis, Pfizer, Samsung, UCB

KFH has been a consultant and advisor for the following companies: AbbVie, LEO Pharma, Novartis and has received speaking fees from: AbbVie, LEO Pharma, Novartis, Janssen, CSL Behring.

KC has served as a paid speaker for Abbvie.

Leuven Research and Development, the technology transfer office of KU Leuven has received consultancy and speaker's fees, and research grants on behalf of RL from Abbvie, Boehringer-Ingelheim, Celgene, Eli-Lilly, Galapagos, Janssen, MSD, Novartis, Pfizer, Samumed and UCB.

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9 Availability of data and material

Not applicable.

10 List of abbreviations

AS: Ankylosing spondylitis

axSpA: Axial spondyloarthritis

CD: Crohns disease

EMA: European Medicines Agency

FDA: U.S. Food and Drug Administration

IBD: Inflammatory bowel disease

IMID: Immune mediated inflammatory disease

MAB: Monoclonal antibody

Nr-axSpA: Non-radiographic axial spondyloarthritis

PsA: Psoriatic arthritis

r-axSpA: Radiographic axial spondyloarthritis

RCT: Randomized controlled trial

SpA: Spondyloarthritis

UC: Ulcerative colitis

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11 Tables

11.1.1 Table 1. Disease entities in the SPEED-UP spectrum and treatment options.

Target		TNF α				TNF α / β	p40	p19 subunit			IL-17A	IL-17RA	CD80/86	α 4 β 7	PDE4	JAK 1/3	
Drug		Adalimumab	Certolizumab	Infliximab	Golimumab	Etanercept	Ustekinumab	Guselkumab	Risankizumab	Tildrakizumab	Secukinumab	Ixekizumab	Brodalumab	Abatacept	Vedolizumab	Apremilast	Tofacitinib
axSpA	R-axSpA	*†	*†	*†	*†	*†					*†	*†					
	Nr-axSpA	*	*†		*	*					*†	*†					
Psoriasis	Plaque	*†	*†	*†		*†	*†	*†	*†	*†	*†	*†	*†			*†	
	Nail	*†					*	*	*		*	*	*			*	
PsA	Peripheral arthritis	*†	*†	*†	*†	*†	*†	†			*†	*†		*†		*†	*†
	Axial arthritis																
	Entesitis																
	Dactylitis																
	Radiographic progression	*†	*	*†	*	*†	*†				*	*		*			
IBD	Crohn's disease	*†	†	*†			*†								*†		
	Fistulating Crohn's disease			*													
	Ulcerative colitis	*†		*†	*†		*†								*†		*†
Uveitis		*†															

Color code	Description
Green	EMA (*) or FDA (†) approved <i>Secondary endpoints are likewise green if mentioned anywhere in the approval document.</i>
Yellow	Primary endpoints met in $\geq$Phase 2 studies. <i>Phase 2 or 3 in which significant results concerning either primary or secondary endpoints.</i>

Red	Contraindicated or to be used with caution <i>Tagged in this category if directly mentioned as a contraindication, or if anywhere else in the approval document mentioned as an inducer of severe adverse effects</i>
Dark grey	Primary endpoint not met in $\geq$Phase 2 studies <i>Tagged in this category if the results describe insignificant results ($p>0,05$).</i>
Light grey	No data or below phase 2 <i>All phase 1 studies were rejected.</i>

12 Figures and legends

Figure 1. A. Illustration of the different treatment targets of drugs with at least one indication by EMA or FDA in the SPEED-UP disease spectrum. B. Illustration of the different TNF inhibitors. C. Illustration of the different IL-23 inhibitors. D. Illustration of the different IL-17 inhibitors. E. Illustration of the mode of action of apremilast including downstream effects on cytokine expression. F. Cytokines signaling via JAK/STAT pathways.

12.1.1