

# Anti-IL-17 Agents in the Treatment of Axial Spondyloarthritis

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**Abstract:** Axial spondyloarthritis (axSpA) describes a group of chronic inflammatory rheumatic diseases primarily involving the axial skeleton. IL-17 is involved in the pathogenesis of numerous inflammatory diseases, including inflammatory arthritis. Until a few years ago, the only biological agents licensed for the treatment of axSpA and nr-axSpA were TNF inhibitors. However, as some patients did not respond to TNF inhibition or experienced secondary failure, the introduction of the first two IL-17 inhibitors (secukinumab [SEC] and ixekizumab [IXE]) has extended the treatment options, and there are now three others (bimekizumab, brodalumab and netakimab) in various stages of clinical development. The last ten years have seen the development of a number of therapeutic recommendations that aimed at improving the management of axSpA patients. The aim of this narrative review of the published literature concerning the role of IL-17 in the pathogenesis of SpA, and the role of IL-17 inhibitors in the treatment of axSpA, is to provide a comprehensive picture of the clinical efficacy and safety of the drugs themselves, and the treatment strategies recommended in the international guidelines.

**Keywords:** spondyloarthritis, ankylosing spondylitis, non radiographic axial spondyloarthritis, axial spondyloarthritis, anti-TNF drugs, anti-IL17 drugs, interleukin 17

## Introduction

The term “axial spondyloarthritis” (axSpA) describes a group of chronic inflammatory rheumatic diseases primarily involving the axial skeleton. These are divided into the two major subtypes of radiographic axSpA (rx-axSpA) or ankylosing spondylitis (AS), and non-radiographic axSpA (nr-axSpA) on the basis of the presence or absence of radiographically detected changes in the sacroiliac joints and/or spine. Both forms are characterised by active inflammation that causes pain, stiffness, and bone formation, and thus leads to severely limited spinal mobility and functional impairment, but they may also involve the entheses and peripheral joints, as well as the eyes, skin and bowel.<sup>1,2</sup>

Nr-axSpA mainly affects females and AS mainly affects males, but there may also be sex-related differences in disease presentation: females often have a high Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and high Patient Global Assessment (PGA) scores, and more frequently experience fatigue and peripheral involvement, whereas males often have high C-reactive protein (CRP) levels, are positive for HLA B27, and show magnetic resonance imaging (MRI) evidence of inflammation.<sup>3–7</sup>

The main aims of axSpA treatment are to decrease inflammation and prevent or slow structural spinal damage in order to reduce pain and stiffness, and preserve

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spinal mobility, and this has led to the introduction of targeted biological agents against TNF and (more recently) IL-17, which are highly effective in reducing disease signs and symptoms, improving physical function, and increasing the quality of life.

The aim of this narrative review of the published literature concerning the role of IL-17 in the pathogenesis of SpA, and the role of IL-17 inhibitors in the treatment of axSpA, is to provide a comprehensive picture of the clinical efficacy and safety of the drugs themselves, and the treatment strategies recommended in the international guidelines.

## The Role of IL-17

IL-17 pro-inflammatory cytokines are produced by CD8<sup>+</sup> T cells,  $\gamma\delta$  T cells, natural killer (NK) T cells, mucosal associated invariant (MAI) T cells, and other cells involved in immune processes.<sup>8</sup> The most widely studied is IL-17A, the expression of which is regulated by other inflammatory cytokines, including IL-23 which, together with IL-17 in the so-called IL-23/IL-17 axis, makes a crucial contribution to host protection and inflammation.<sup>9,10</sup>

IL-17 is involved in the pathogenesis of numerous inflammatory diseases, including inflammatory arthritis,<sup>10,11</sup> and its effects on specific cells (eg fibroblasts, epithelial cells and synoviocytes) lead to the transcription of pro-inflammatory genes and the subsequent secretion of pro-inflammatory cytokines (TNF, IL-1, IL-6) and chemokines (CCL20, CCL2, CCL7, CXCL1, CXCL2, CXCL5, CXCL8).<sup>12–15</sup> It also increases the production of granulomatosis-stimulating factors (G-CSF, GM-CSF),<sup>16</sup> and regulates the production of antimicrobial peptides (defensins and S100 proteins).<sup>17</sup> However, despite its protective function, excessive activation of the IL-17 pathway can lead to autoimmune responses or inflammatory diseases:<sup>18</sup> it can guide the degradation of the joint extracellular matrix in patients with inflammatory arthritis;<sup>19,20</sup> cause osteoclast activation and bone destruction;<sup>21</sup> and also promote the angiogenesis that allows inflamed joints to be reached by inflammatory cells.<sup>22,23</sup>

IL-17F plays a similar role to that of IL-17A, but induces a weaker inflammatory response.<sup>24</sup> It increases the production of certain pro-inflammatory mediators and matrix metalloproteinases in fibroblasts and epithelial cells,<sup>25,26</sup> and is involved in the neutrophilia associated with severe asthma.<sup>27</sup>

IL-17A and IL-17F therefore both have pro-inflammatory, osteoclastogenic and angiogenic potential, thus making them critical drivers of inflammation.<sup>18</sup>

The IL-23/IL-17 axis plays a clear role in the pathogenesis of SpA.<sup>18</sup> Taams et al have reviewed its role in animal models of inflammatory arthritis, discussed the presence of IL-17 family members in the blood and tissue of SpA patients, and investigated the genetic variants involving the axis that leading to susceptibility to SpA.<sup>18</sup> They have also explored the synergistic effect of IL-17 and other pro-inflammatory cytokines on joint inflammation and altered bone homeostasis.<sup>18</sup>

A number of animal models of inflammatory arthritides, including rheumatoid arthritis (RA) and SpA, have demonstrated the key pathogenetic role of the IL-17 and IL-23 pathways.<sup>18</sup> It has been shown that the inhibition of IL-17A decreases disease activity and joint damage in an adjuvant-induced model of arthritis.<sup>28,29</sup> Moreover, IL-17 or IL-17 receptor knockout in an animal model of collagen-induced arthritis (CIA) prevents the development of the disease, which depends on IL-17 in its early phases, is partially suppressed by IL-17 receptor inhibition during the phase of active inflammation, and is exacerbated in terms of severity and joint destruction when IL-17 is overexpressed.<sup>30–33</sup>

One comprehensive review of these animal models<sup>34</sup> has reported that the overexpression of HLA-B27 in rats leads to the proliferation of IL-17<sup>+</sup> CD4<sup>+</sup> T cells.<sup>35,36</sup> It has also been shown that the IL-17 produced by IL-23 stimulates arthritis within an SpA syndrome in the SKG mouse model of RA,<sup>37–39</sup> and that the introduction of exogenous IL-23 stimulates the production of IL-17 and exacerbates enthesitis in the CIA model.<sup>40,41</sup> Furthermore, IL-17 plays a key role in the development of ankylosis and psoriasis-like dermatitis in certain mouse strains.<sup>42,43</sup>

## IL-17A and IL-17F Cytokines in SpA Patients

IL-17A and IL-17F have been investigated in fewer studies of SpA than studies of RA, but the results have shown that their serum levels are significantly higher in SpA patients than in healthy subjects.<sup>43,44</sup> Moreover, serum IL-17 levels in AS patients correlate positively with disease activity.<sup>45,46</sup> It has also been found that IL-17 levels are higher in the synovial fluid than in the serum of psoriatic arthritis (PsA) patients,<sup>47</sup> and higher in the synovial fluid of patients with reactive arthritis or

undifferentiated SpA than in those with osteoarthritis (OA) or RA.<sup>48</sup> Furthermore, the expression of IL-17 receptor A is higher in the synoviocytes of PsA and RA patients than in the synoviocytes of patients with OA.<sup>49</sup>

One study has found that the gut (terminal ileum) of AS patients is a significant source of IL-23 but not IL-17.<sup>50</sup>

The only data available concerning IL-17F in SpA patients show that it is more frequently present and more expressed in the synovial tissue of patients with PsA than in OA patients.<sup>51,52</sup>

The synergistic effects of IL-17A and other cytokines and mediators lead to an increased pro-inflammatory response and, although these effects have been explored in only a few studies of SpA, they have been widely studied in RA patients.<sup>18</sup>

The most widely studied is the synergy of IL-17A and TNF.<sup>53–55</sup>

However, the synergistic role of IL-17A and TNF in bone formation and destruction still needs further and more detailed clarification.<sup>18</sup>

IL-17A can also have synergistic effects with other pro-inflammatory cytokines:<sup>18</sup> together with IL-1 $\beta$ , it increases the production of IL-6 by RA synoviocytes<sup>56</sup> and the production of CCL20 by fibroblast-like synoviocytes<sup>57</sup> and, together with IFN $\alpha$ , it enhances the expression of intercellular adhesion molecule 1 (ICAM1), thus increasing inflammation in PsA patients.<sup>58</sup>

The lack of robust evidence means that the role of IL-17F in the pathogenesis of SpA still needs to be definitely confirmed,<sup>18,59</sup> but it is known that it acts synergistically with IL-17A in the process of inflammation<sup>52,59</sup> and it has been shown that dual IL-17A and IL-17F blockade reduces inflammation better than IL-17A blockade alone.<sup>59</sup>

The mechanisms allowing the synergistic effects of IL-17A and IL-17F are not clear, but it has been hypothesised that IL-17A may stabilise mRNA transcripts, thus increasing gene expression and protein production,<sup>60</sup> and that phospholipase D enzymes may up-regulate cytokine secretion.<sup>61</sup> For example, although there is no evidence concerning IL-17F,<sup>18</sup> it has been reported that IL-8 mRNA and other mRNA transcripts (including ACT1, MIP2 and CSF2) are involved in the synergy between TNF and IL-17A.<sup>15,18</sup>

Among all of the immunity cell types capable of producing IL-17, it has been shown that a number of T cell subsets produce IL-17 in patients with SpA.<sup>11,62–64</sup>

1. IL-17<sup>+</sup> CD8<sup>+</sup> T cells have been identified as potential sources of IL-17 in studies of immune-mediated inflammatory diseases, including psoriasis, multiple sclerosis and PsA (eg in psoriatic skin lesions).<sup>58,62,65–70</sup> These T cells can be found in the peripheral blood of patients with AS, and their frequency increases with the severity of the disease;<sup>71</sup> furthermore, they are more frequent in the synovial fluid than in the peripheral blood of both PsA and AS patients.<sup>65,72</sup> Their immunophenotype shows pro-inflammatory capacity,<sup>73</sup> and their presence is associated with markers of disease activity such as CRP levels and Doppler findings.<sup>65</sup> However, increased levels of IL-17-producing CD8<sup>+</sup> T cells have not been found in RA patients,<sup>65</sup> and seem to be related to the development of only HLA class I and not HLA class II-associated SpA.<sup>18</sup>
2. Tissue-resident memory (T<sub>RM</sub>) T cells. CD8<sup>+</sup> T<sub>RM</sub> cells express IL-17 and other cytokines in the skin of healthy and psoriatic subjects<sup>69,74–76</sup> and, although less widely studied, CD4<sup>+</sup> T<sub>RM</sub> cells have also been found in human skin.<sup>77</sup> It has been shown that IL-17-producing T<sub>RM</sub> cells can be considered disease drivers in a mouse model of SpA,<sup>78</sup> and they may be present in the synovial fluid of patients with juvenile inflammatory arthritis (JIA)<sup>79</sup> or SpA,<sup>73</sup> which underlines their importance in the pathogenesis of inflammatory arthritides.<sup>18</sup>
3. MAIT cells. CD8<sup>+</sup> MAIT cells (particularly Va7.2/IL-17<sup>+</sup>CD8<sup>+</sup> T cells) have been identified in the skin and blood of psoriatic patients.<sup>80,81</sup> They are also more frequently detected in the peripheral blood of AS patients than in the peripheral blood of healthy subjects.<sup>82,83</sup>
4. Invariant NKT cells. Very few studies have described the presence of IL-17-producing NKT cells in SpA patients, but the findings of a murine study suggest that NKT cells may maintain or activate T<sub>H</sub>17 cells, and thus contribute to the development of inflammation.<sup>84</sup>
5.  $\gamma\delta$  T cells producing IL-17 have been very frequently detected in the peripheral blood of patients with PsA, AS, reactive arthritis, and enthesitis-related JIA,<sup>78,85–87</sup> as well as in the synovial fluid of patients with PsA, reactive arthritis, and undifferentiated SpA.<sup>87,88</sup> It has also been shown that  $\gamma\delta$  T cells produce IL-17 in mouse models of SpA and psoriatic skin inflammation,<sup>89–91</sup> and accumulate in

tissues often affected by SpA, such as the entheses, the aortic root, and the eye.<sup>92</sup>

### Other Cells

IL-17 can also be produced by immunity cells other than T cells, including group 3 innate lymphoid cells (ILC3s), which have been described in the peripheral blood and synovial fluid of PsA patients, where their levels correlate with disease activity.<sup>93,94</sup> High levels of CD3<sup>+</sup> CD56<sup>+</sup> NK cells have been detected in patients with enthesitis-related arthritis,<sup>86</sup> and IL-17-producing NK cells have been found in the synovial fluid of patients with reactive arthritis or undifferentiated SpA.<sup>88</sup>

Finally, it has been found that mast cells, which were initially hypothesized to be IL-17 producing cells, actually have the function of storing and releasing exogenous IL-17A.<sup>95,96</sup>

## IL-17 Inhibition in axSpA Patients: Randomised Controlled Trials and Real-Life Data

Until a few years ago, the only biological agents licensed for the treatment of AS and nr-axSpA were TNF inhibitors. However, as some patients did not respond to TNF inhibition or experienced secondary failure, the introduction of the first two IL-17 inhibitors (secukinumab [SEC] and ixekizumab [IXE]) has extended the treatment options, and there are now three others (bimekizumab, brodalumab and netakimab) in various stages of clinical development.<sup>97</sup>

The last ten years have seen the development of a number of therapeutic recommendations aimed at improving the management of axSpA patients. The guidelines of the Assessment of Spondyloarthritis International Society/European League Against Rheumatism (ASAS/EULAR)<sup>98</sup> and those of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (ACR/SAA/SPARTAN)<sup>99</sup> recommend the use of non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy in the first-line treatment of pain and stiffness.

As for conventional disease-modifying anti-rheumatic drugs (DMARDs), only sulfasalazine has demonstrated a mild efficacy in treating the axial manifestations of SpA but, as well as methotrexate and leflunomide, it may play a role in the treatment of peripheral SpA solely.

In the case of non-responders to NSAIDs or patients for whom NSAIDs are contraindicated, biological drugs (TNF and IL-17 inhibitors) are strongly recommended. As there is no indication that any one of these is more effective than the others, the choice should be made on the basis of the available safety data, the presence of extra-articular manifestations, and patient preference. Since no predictive factors of good response to IL-17 inhibitors are currently available, treatment response is still far from ideal for many patients, and we lack the biomarkers to predict which medication is most appropriate for an individual patient. The ASAS/EULAR<sup>98</sup> and ACR/SAA/SPARTAN<sup>99</sup> guidelines recommend TNF inhibitors as first line of biologic agents, mainly because of a broader clinical experience and larger pharmacovigilance data with these agents as compared to IL-17 inhibitors. This approach may change in future when real life data and results of comparative and strategy studies on IL-17 inhibitors will be available.

Clinical trials are of course the gold standard for assessing the efficacy and safety of new biological drugs but, as they are conducted under standardized conditions and exclude certain types of patients and/or situations, their findings may not reflect their real-world prescription and use.

### Secukinumab

The efficacy and safety of SEC, a fully human antibody that selectively targets IL-17A and inhibits its interaction with IL-17 receptors,<sup>100</sup> has been tested in AS patients in one phase II<sup>101</sup> and five Phase III trials (MEASURE 1,<sup>102</sup> MEASURE 2,<sup>103</sup> MEASURE 2-J,<sup>104</sup> MEASURE3<sup>105</sup> and MEASURE4<sup>106</sup>) and their extensions. In the Phase II proof-of-concept study, 59% of the patients in the SEC group showed a week-64 ASAS20 response as against 24% of the patients receiving placebo (PBO).

MEASURE 1 and 2,<sup>97</sup> which respectively enrolled 371 and 219 patients, tested two doses of the active drug (75 and 150 mg) against PBO, and had the percentage of patients with a week-16 ASAS20 response as their primary endpoint (Table 1). At the end of the MEASURE 1 study, an ASAS20 response was achieved by 61% of the patients in the 75 mg group, 60% of those in the 150 mg group, and 28% of those in the PBO group; in MEASURE 2, the corresponding figures were respectively 41%, 61% and 28%.<sup>102,103</sup> The drug was efficacious regardless of whether it was received by patients as their first biological drug or by patients failing to respond to previous anti-TNF

**Table I** Summary of Secukinumab Trials

	<b>MEASURE1<sup>102</sup></b> (TNFi-Naïve and TNFi-IR As Patients)	<b>MEASURE2<sup>103</sup></b> (TNFi-Naïve and TNFi-IR As Patients)	<b>MEASURE3<sup>105</sup></b> (TNFi-Naïve and TNFi-IR As Patients)	<b>PREVENT<sup>114</sup></b> (nr-axSpA Patients)
Subjects	371	219	226	555
Drug regimen	i.v. SEC 10 mg/kg or matched PBO week 0, 2 and 4, and then s.c. SEC (75 or 150 mg) or matched PBO injection every 4 weeks, starting week 8	s.c. SEC (75 or 150 mg) or matched PBO week 0, 1, 2, 3 and 4, and then every 4 weeks	i.v. SEC 10 mg/kg or matched PBO week 0, 2 and 4, and then s.c. SEC (150 or 300 mg) or matched PBO injection every 4 weeks starting week 8	SEC 150 mg LD, SEC 150 mg NL, or PBO week 0, 1, 2 and 3, and then every 4 weeks starting week 4. The SEC 150 mg NL group received PBO in week 1, 2, and 3 to maintain blinding
ASAS20 responses week 16 (primary endpoint of MEASURE 1, 2 and 3; secondary endpoint of PREVENT)	60% (SEC 150 mg)* 61% (SEC 75 mg)* 29% (PBO)	61% (SEC 150 mg)* 41% (SEC 75 mg) 28% (PBO)	60.5% (SEC 300 mg)* 58.1% (SEC 150 mg)** 36.8% (PBO)	56.8% (SEC 150 mg LD)** 58.2% (SEC 150 mg ND)** 45.7% (PBO)
ASAS40 responses week 16 (secondary endpoint of MEASURE 1, 2 and 3; primary endpoint of PREVENT)	42% (150 mg)* 33% (75 mg)* 13% (PBO)	36% (SEC 150 mg)* 26% (SEC 75 mg) 11% (PBO)	42.1% (SEC 300 mg)** 40.5% (SEC 150 mg)** 21.1% (PBO)	41.5% (SEC 150 mg LD)** 40.8% (SEC 150 mg ND)* 29.2% (PBO)
ASAS-PR week 16	15% (SEC 150 mg)* 16% (SEC 75 mg)* 3% (PBO)	14% (SEC 150 mg)* 15% (SEC 75 mg)* 4% (PBO)	21.1% (SEC 300 mg)** 9.5% (SEC 150 mg) 1.3% (PBO)	21.6% (SEC 150 mg LD)* 21.2% (SEC 150 mg ND)* 7% (PBO)

**Notes:** \*P<0.01, \*\* P<0.05 in comparison with placebo.

**Abbreviations:** AS, ankylosing spondylitis; nr-axSpA, non radiographic axial spondyloarthritis; TNFi, tumour necrosis factor inhibitors; IR, inadequate responders; SEC, secukinumab; i.v., intravenous; s.c., subcutaneous; LD, loading dose; NL, no loading dose; PBO, placebo; PR, partial remission.

treatment. About 80% of the patients did not experience radiographic progression over a period of two years,<sup>107</sup> and the drug was well tolerated.<sup>108</sup>

Sustained responses were observed in the 5-year, long-term extension of MEASURE 1, during which 74% of the patients in the 75 mg group and 79% of those in the 150 mg group achieved an ASAS20 response, and respectively 54% and 65% achieved an ASAS40 response.<sup>109,110</sup> Among the 150 patients who completed five years' treatment with SEC 150 mg in the extension of MEASURE 2,<sup>111</sup> ASAS20 responses were recorded in 67% and ASAS40 responses in 50%, and there were sustained improvements in the other efficacy endpoints. The drug's safety profile remained consistent with that described in previous reports.<sup>111</sup>

A pooled analysis of MEASURE 1 and 2 showed that the majority of the SEC-treated patients who achieved

remission by week 16 remained in remission for up to three years.<sup>112</sup>

The use of SEC 150 mg in the MEASURE 2-J trial led to sustained improvement in the signs and symptoms of Japanese AS patients for 24 weeks without giving rise to any new or unexpected safety issues.<sup>104</sup>

In the MEASURE 3 trial, in comparison with 36.8% of the patients receiving PBO, a 16-week ASAS20 response (the primary endpoint) was observed in 60.5% of the patients treated with SEC 300 mg (p<0.01) and 58.1% of those treated with SEC 150 mg (p<0.05).<sup>105</sup> There were improvements in the primary and secondary endpoints in both TNF inhibitor-naïve patients and patients inadequately responding to previous TNF inhibition.<sup>113</sup> The 52-week ASAS20 and ASAS40 response rates in the SEC 150 mg group were respectively 54% and 41%.<sup>105</sup>



MEASURE 4 assessed the long-term efficacy, safety and tolerability of SEC. The initial 16-week treatment was completed by 97% of the patients, and the subsequent two-year treatment was completed by 83%.<sup>106</sup> The primary endpoint of 16-week ASAS20 responses was not reached because of the very high response rate in the PBO group,<sup>109</sup> but the drug's two-year safety profile matched that described in previous studies.<sup>113</sup>

PREVENT was the first phase III trial of SEC in active nr-axSpA patients with objective signs of inflammation (MRI with SI joint inflammation and/or high-sensitivity CRP).<sup>114</sup> The treatment improved disease signs and symptoms throughout the 52-week study period without leading to any new safety findings. The study met both of its primary endpoints: the 16-week ASAS40 response rate was higher among the patients receiving SEC 150 mg with loading doses than among those receiving PBO (41.5% vs 29.2%;  $p = 0.0197$ ), and the 52-week ASAS40 response rate was also higher in the patients receiving SEC 150 mg without loading doses (39.8% vs 19.9%;  $p < 0.0021$ ).<sup>114</sup>

A very recent systematic review and meta-analysis of ten randomized controlled trials (RCTs) assessing the efficacy and safety of IL-17A inhibitors in a total of 2,613 patients with AS (six trials of SEC, two of IXE, and one each of netakimab and bimekizumab) showed that, in comparison with placebo, the IL-17A inhibitors improved both the ASAS20 response rate (OR = 2.58;  $p < 0.01$ ) and the ASAS40 response rate (OR = 2.80;  $p < 0.01$ ). Although the treatment significantly increased the risk of adverse events (OR = 1.23;  $p = 0.03$ ) and nasopharyngitis (OR = 1.72;  $p < 0.01$ ), it did not increase the risk of serious adverse events (OR = 0.87;  $p = 0.60$ ).<sup>115</sup>

In 2018, Gentileschi et al described the first real-life experience of the short-term efficacy of SEC in 21 axSpA patients enrolled at three Italian referral centers. Between the start of treatment and the 3-month follow-up visit, there was a statistically significant reduction in the BASDAI ( $p < 0.0001$ ) and ASDAS-CRP values ( $p = 0.0005$ ), with no statistically significant difference between the subgroups receiving SEC 150 or 300 mg, and no significant difference between the biological treatment-naïve patients and the patients previously treated with TNF inhibitors. No adverse events were reported during the observation period.<sup>116</sup>

The same group also published the findings of a real-life study of the long-term effectiveness of SEC and drug survival in axSpA patients in 2020. There was

a statistically significant reduction in the BASDAI and ASDAS-CRP values during the 24-month observation period, with no statistically significant difference between the two doses or between the biological treatment-naïve patients and the patients failing to respond to previous TNF inhibition. The global 24-month drug retention rate was 78.2%, and no adverse event or infectious disease was reported during the study period.<sup>117</sup>

In 2019, Mann et al published findings taken from the Czech ATTRA that showed rheumatologists considered SEC to be equivalent to a TNF inhibitor in the case of biological DMARD-naïve patients and that, after the failure of  $\geq 3$  TNF inhibitors, patients were significantly more likely to be treated with SEC.<sup>118</sup>

Elliot and Wright described their experience with SEC in a cohort of 45 patients: 36 with PsA (five of whom had predominant axial disease) and nine with AS. SEC proved to be effective in patients inadequately responding to TNF inhibition in their clinical setting.<sup>119</sup>

Williams et al described the results of their real-world experience of SEC treatment for AS at the Royal National Hospital for Rheumatic Diseases in Bath in 2020, thus providing further evidence that SEC is largely safe and effective.<sup>120</sup>

Also, in 2020, the Spondyloarthritis Roman Group (STRONG) published the results of a multicentre, prospective observational study<sup>121</sup> showing that SEC improved all of the evaluated clinical parameters and patient-reported outcomes after six and 12 months. The treatment was well tolerated, and drug survival was good, particularly among male AS patients.<sup>121</sup>

Another real-life study of 1,860 axSpA patients in 13 European registries participating in the European Spondyloarthritis Research Collaboration Network was published in 2020.<sup>122</sup> SEC retention rates after six and 12 months of treatment were respectively 82% and 72%, and comparable with those observed in studies of TNF inhibition. Response rates were lower than those recorded in the RCTs but consistently better among the biological drug-naïve patients.<sup>122</sup>

A recent systematic review and meta-analysis of real-life studies of the biological drugs used to treat AS has shown that one-year drug survival rate of SEC was 0.77 (95% confidence interval 0.64–0.90).<sup>123</sup>

A Canadian cost-effectiveness analysis has shown that SEC 150 mg is a more cost-effective option for biological treatment-naïve AS patients than certolizumab pegol, adalimumab, golimumab, etanercept and an etanercept

biosimilar, or infliximab and an infliximab biosimilar,<sup>124</sup> and the situation is similar in Finland<sup>125</sup> and the UK<sup>126</sup> for both biological treatment-naïve and biological treatment-experienced patients with active AS.

The ongoing, longitudinal SERENA study of patients with psoriasis, PsA or AS with an observational period of up to five years is being conducted at 438 centers across Europe and, when its results become available, it will provide valuable information concerning the long-term, real-world effectiveness and safety of SEC.<sup>127</sup>

Two recent real life cohort studies compared effectiveness of treatment with SEC with that of TNF inhibitors. Both studies showed that axSpA patients with prior TNFi exposure treated with SEC experienced comparable outcomes as patients treated with an alternative TNF inhibitor.<sup>128,129</sup>

## Ixekizumab

The efficacy of IXE, an IgG4 monoclonal antibody that has affinity for the homodimer IL-17A and the heterodimer IL-17A/F, in treating radiographic axSpA has been demonstrated in two phase III RCTs (COAST-V<sup>130</sup> and COAST-W<sup>131</sup>), both of which achieved their primary

endpoints and showed significant ASAS40 responses to its administration every two or every four weeks (Table 2).

In the COAST-V trial, which enrolled TNF inhibitor-naïve AS or r-axSpA patients, 16-week ASAS40 responses were observed in 51.8% of those receiving IXE every two weeks, in 48.1% of those receiving IXE every four weeks, and in 18.6% of those receiving PBO.<sup>130</sup> The trial also included a fourth study arm of patients receiving adalimumab 40 mg every two weeks that served as an in-study active reference for comparison. Numerically, the ASAS40 response seen with IXE were similar to those observed in the adalimumab group. Week-52 ASAS40 responses were observed in 53.1% of the patients treated with IXE every 4 weeks and in 51% of the patients treated with IXE every 2 weeks.<sup>131–134</sup>

The COAST-W trial enrolled AS or r-axSpA patients inadequately responding to TNF inhibition. Week-16 and week-52 ASAS40 responses were observed in respectively 25.4 and 34.2% of the patients treated with IXE every four weeks, 30.6 and 30.6% of those treated with IXE every two weeks.<sup>131,134</sup>

No data are yet available concerning the ability of IXE to inhibit structural progression.

**Table 2** Summary of Ixekizumab Trials

	<b>COAST-V<sup>130</sup></b> (TNFi Naïve r-axSpA Patients)	<b>COAST-W<sup>131</sup></b> (TNFi-IR r-axSpA Patients)	<b>COAST-X<sup>135</sup></b> (nr-axSpA Patients)
Subjects	341	316	303
Drug regimen	s.c. IXE 80 mg every 2 or every 4 weeks; s.c. ADA 40 mg every 2 weeks (active reference group); or matching PBO injection every 2 weeks	s.c. IXE 80 mg every 2 or every 4 weeks; matching PBO injection every 2 weeks	s.c. IXE 80 mg every 2 or every 4 weeks; matching PBO injection every 2 weeks
ASAS20 response week 16 (secondary endpoint)	68.7% (IXE 80 mg Q2W)* 64.2% (IXE 80 mg Q4W)* 60.5% (ADA 40 mg Q2W) 40.7% (PBO)	46.9% (IXE 80mg Q2W)** 48.2% (IXE 80mg Q4W)** 29.8% (PBO)	NA
ASAS40 response week 16 (primary endpoint)	51.8% (IXE 80 mg Q2W)† 48.1% (IXE 80 mg Q4W)† 36% (ADA 40 mg Q2W) 18.6% (PBO)	30.6% (IXE 80mg Q2W)‡ 25.4% (IXE 80mg Q4W)‡ 12.5% (PBO)	40% (IXE 80 mg Q2W)# 35% (IXE 80 mg Q4W)# 19% (PBO)
ASAS-PR week 16	14.5% (IXE 80 mg Q2W) 14.8% (IXE 80 mg Q4W) 15.1% (ADA 40 mg Q2W) 8.1% (PBO)	5.1% (IXE 80 mg Q2W) 6.1% (IXE 80 mg Q4W) 1.1% (PBO)	NA

**Notes:** †P<0.0001 (Q2W and Q4W); ‡P=0.003 (Q2W), P=0.017 (Q4W); \*P= 0.002 (Q2W), P=0.0015 (Q4W); \*\*P<0.05 (Q2W), P<0.01 (Q4W); #P=0.0094 (Q4W), P=0.0016 (Q2W); P values in comparison with placebo.

**Abbreviations:** r-axSpA, radiographic axial spondyloarthritis; nr-axSpA, non radiographic axial spondyloarthritis; TNFi, tumour necrosis factor inhibitors; IR, inadequate responders; NSAIDs, non-steroidal anti-inflammatory drugs; IXE, ixekizumab; s.c., subcutaneous; PBO, placebo; ADA, adalimumab; NA, not available; Q2W, every two weeks; Q4W, every four weeks; PR, partial remission.

The efficacy and safety of IXE in patients with nr-axSpA was assessed in the COAST-X trial, a phase III RCT that enrolled TNF inhibitor-naïve patients<sup>135</sup> (Table 2). IXE was superior to PBO after 16 and 52 weeks: 16-week ASAS40 responses were observed in 35% of the patients receiving IXE every four weeks, 40% of those receiving IXE every two weeks, and 19% of those receiving PBO; 52-week ASAS40 responses were observed in respectively 30%, 31%, and 13%. The adverse events were no different from those found in previous IXE studies, and no new safety issues were identified.<sup>136</sup> IXE was approved for the treatment of nr-axSpA by the FDA and the EMA in June 2020.<sup>137</sup>

To the best of our knowledge, there are no published real-life observational studies of IXE treatment in axSpA patients.

### Efficacy of Secukinumab and Ixekizumab on Extra-Axial Manifestations

In addition to axial involvement, axSpA patients may also suffer from peripheral arthritis, enthesitis and dactylitis as well as extra-articular manifestations such as psoriasis, uveitis and inflammatory bowel diseases (IBD). These outcomes have not been specifically assessed in the above mentioned SEC and IXE pivotal trials where only axial outcomes have been studied as primary endpoints.

Nevertheless, some information about peripheral arthritis, enthesitis, dactylitis and psoriasis may be drawn from the development programs of IXE and SEC in PsA showing significant improvements for all these features.<sup>113</sup>

Treatment emergent anterior uveitis and IBD were reported in long-term clinical trials (MEASURE and COAST programs) and post marketing safety data in psoriasis, PsA and AS with low overall incidences, within the expected ranges in these disorders.<sup>110,111,134,138</sup> However, the available data, although limited, would encourage caution in the use of IL-17 inhibition in patients with a history of uveitis or IBD.

Based on the aforementioned data regarding uveitis, IBD and psoriasis, IL-17 inhibitors would not be the first choice in case of associated IBD or uveitis, whereas it would be appropriate in case of psoriasis.

### Other IL-17 Inhibitors

Brodalumab (an IL-17A receptor antagonist that also inhibits IL-17F, the IL-17A/F heterodimer and IL-17E) is approved for the treatment of psoriasis.<sup>139</sup> However, a phase III trial involving patients with PsA was interrupted because of

concerns about major side effects including depression and suicidal behaviour<sup>140</sup> (although it is still unclear whether there is a causal relationship between the drug and suicidal ideation and behaviour), and a PBO-controlled phase II trial involving axSpA patients (ClinicalTrials.gov ID NCT02429882) was cancelled and withdrawn in 2015.

The preliminary results of a phase III trial of brodalumab treatment in AS and nr-axSpA patients (ClinicalTrials.gov ID NCT02985983) carried out in Japan were presented at the 2019 EULAR conference.<sup>141</sup> The week-16 ASAS40 response rate was significantly higher in the brodalumab group (35/80, 43.8%,  $p=0.018$ ) than in the PBO group (19/79, 24.1%) and, on the basis of these results, brodalumab may be considered a future therapeutic option for patients with axSpA.

Bimekizumab, an inhibitor of both IL-17A and IL-17F, has been shown to be effective in a phase IIb trial involving AS patients:<sup>142</sup> significantly more bimekizumab-treated patients achieved a week-12 ASAS40 response than those receiving PBO (non-responder imputation: 29.5% for bimekizumab 16 mg every four weeks; 42.6% for bimekizumab 64 mg every four weeks; 46.7% for bimekizumab 160 mg every four weeks vs 13.3% for PBO every four weeks;  $p<0.05$ ).<sup>132</sup> Phase II trials involving AS patients (ClinicalTrials.gov ID NCT03355573 and NCT03215277) and phase III trials involving patients with AS (ClinicalTrials.gov ID NCT03928743), nr-axSpA (ClinicalTrials.gov ID: NCT03928704), or AS and nr-axSpA (ClinicalTrials.gov ID NCT04436640) are currently ongoing.

Netakimab is a recombinant humanized IgG1 anti-IL-17 monoclonal antibody with a modified Fc fragment and CDR regions.<sup>143</sup> A Phase III, PBO-controlled trial (ClinicalTrials.gov ID NCT03447704) is currently evaluating the safety and efficacy of a 120 mg dose for up to one year in 228 patients with active AS.

### Conclusions

The IL-23/IL-17 axis plays a clear role in the pathogenesis of SpA. IL-17A and IL-17F have been investigated in few studies of SpA, but their serum levels are significantly higher in SpA patients and correlate positively with disease activity. TNF and (more recently) IL-17 inhibitors have dramatically changed the scenario of axSpA treatment as they are highly effective in reducing disease signs and symptoms, improving physical function, and increasing the quality of life. The results of clinical trials have shown that IL-17 inhibitors are efficacious and safe, and this has been confirmed by some recent real-world data



concerning a range of unselected patients. The guidelines of the ASAS/EULAR and those of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (ACR/SAA/SPARTAN) recommend in the case of non-responders to NSAIDs or patients for whom NSAIDs are contraindicated, biological drugs (TNF and IL-17 inhibitors). Until today, there is no indication that any one of these is more effective than the others, then the choice should be made on the basis of the available safety data, the presence of extra-articular manifestations, and patient preference. However, based on the published data IL-17 inhibitors would not be the first choice in case of associated IBD or uveitis.

## Disclosure

Dr Salvatore D'Angelo reports personal fees from Abbvie, Eli Lilly, Novartis, and UCB, outside the submitted work. The authors reported no other potential conflicts of interest for this work.

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