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Interleukin-17 inhibitors for the treatment of ankylosing spondylitis

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Abstract

Tumor necrosis factor inhibitor (TNFi) has been applied in the treatment of ankylosing spondylitis (AS) for many years but still with an unmed need due to inefficacy or intolerance. Current treatment guideline recommended the use of IL-17 inhibitors over a second TNFi in patients with primary nonresponse to the first TNFi. We herein review the present available IL-17 inhibitors including secukinumab (SEC), ixekizumab (IXE), brodalumab and bimekizumab (BKZ) in clinical trials of AS. Therapeutic response and safe profile have been discussed in detail for each drug. Overall, IL-17 inhibitors were proved to be alternatives for biologic disease-modifying anti-rheumatic drugs (bDMARDs) in AS, which might be safer for tuberculosis while candida infection should be monitored in long term treatment.

Keywords

interleukin-17 inhibitor • ankylosing spondylitis • tumor necrosis factor inhibitor • efficacy • safety

Introduction

The advent of biologic disease-modifying antirheumatic drugs (bDMARDs) has been considered as the breakthrough in the treatment of ankylosing spondylitis (AS). Nonetheless, there is still an unmet need concerning that up to 40% of patients do not respond sufficiently to tumor necrosis factor (TNF) inhibitor (TNFi).[1] Current treatment guideline recommended the use of interleukin (IL)-17 inhibitors including secukinumab (SEC) or ixekizumab (IXE) over a second TNFi in patients with primary nonresponse to the first TNFi.[2]

Secukinumab in AS

There are 12 studies presented on clinicaltrials.gov with available data on 16 Week Efficacy and 2 Year Long Term Safety and Efficacy of Secukinumab in Patients With Active Ankylosing Spondylitis (MEASURE 1-4) study.

In MEASURE 1[3] (NCT01358175), a total of 371 patients received intravenous SEC (10 mg/kg of body weight) or matched placebo at Weeks 0, 2, and 4, followed by subcutaneous SEC (150 or 75 mg) or matched placebo every 4 weeks starting at Week 8. The Assessment of Spondyloarthritis International Society (ASAS) 20 response rates at Week 16 were 61%, 60%, and 29% for subcutaneous SEC at doses of 150 and 75 mg and for placebo, respectively. SEC provided significant and sustained improvements in patient-reported disease activity, health-related quality of life (QoL), and reduced functional impairment, fatigue, and impact of disease on work productivity through 52 weeks,[4] with a low mean progression of spinal radiographic changes through 2 years.[5] In the extension trial (NCT01863732), SEC provided sustained efficacy on signs and symptoms and magnetic resonance

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imaging (MRI) outcomes, a low rate of radiographic progression through 4 years.[6] And SEC 150 mg provided sustained efficacy across multiple domains through 5 years.[7]

In MEASURE 2[3] (NCT01649375), a total of 219 patients received subcutaneous SEC (150 or 75 mg) or matched placebo at baseline; at Weeks 1, 2, and 3; and every 4 weeks starting at Week 4. The ASAS 20 rates were 61%, 41%, and 28% for subcutaneous SEC at doses of 150 and 75 mg and for placebo, respectively. In the post hoc analysis of pooled data for 3 years of MEASURE 1 and 2, SEC 150 mg demonstrated rapid and sustained efficacy irrespective of baseline C reactive protein (CRP), with greater magnitude of response in patients with more elevated CRP.[8] SEC 150 mg provided sustained improvements in signs and symptoms in anti-tumor necrosis factor (TNF)-naïve and anti-TNF-IR patients through 52 weeks.[9] SEC provided sustained improvement through 2 years in the signs and symptoms of AS.[10]

In MEASURE 3[11] (NCT02008916), a total of 226 patients were randomized to receive intravenous SEC 10 mg/kg (baseline and Weeks 2 and 4) followed by subcutaneous SEC 300 mg intraveneous (IV-300 mg) or 150 mg (IV-150 mg) every 4 weeks, or matched placebo. The ASAS 20 response rate was significantly greater at Week 16 in the IV-300 mg (60.5%; $P<0.01$) and IV-150 mg (58.1%; $P<0.05$) groups versus placebo (36.8%). Improvements achieved with SEC in all clinical end points at Week 16 were also sustained at Week 52.

In MEASURE 4[12] (NCT02159053), a total of 350 patients with active AS were randomized (1:1:1) to receive subcutaneous SEC 150 mg with loading dose (150 mg), without loading dose (150 mg no load), or placebo. All patients received SEC or placebo at baseline; Weeks 1, 2, and 3; and every 4 weeks starting at Week 4. The ASAS 20 response rate at Week 16 was 59.5% and 61.5% with 150 and 150 mg no load groups, respectively, versus placebo (47%; $P=0.057$ and 0.054, respectively); the primary end point was not met. Increases in response rates achieved with SEC for ASAS 20 at Week 16 were sustained through Week 104.

The first study Effect of Secukinumab on Radiographic Progression in Ankylosing Spondylitis as Compared to GP2017 (Adalimumab Biosimilar) (SURPASS)[13] designed to evaluate superiority of SEC over a TNFi, SDZ-ADL, GP2017 (adalimumab biosimilar), in reducing spinal radiographic progression in AS (NCT03259074) was started on October 24, 2017. Study estimating the clinical difference between 300 and 150 mg of SEC following dose escalation to 300 mg in patients with AS (ASLeap) (NCT03350815) has been recruiting since March 13, 2018. A Japanese study with a small sample size (NCT02750592) that evaluated the efficacy and safety in active AS has completed, with pending publication. A randomized, double-blind, placebo-controlled multicenter study of SEC (AIN457) to examine the clinical efficacy and the nonsteroidal anti-inflammatory drug (NSAID)-sparing effect in AS A Randomized, Double-blind, Placebo-controlled Multicenter Study of Secukinumab (AIN457) to Examine the Clinical Efficacy and the Nonsteroidal Anti-inflammatory Drug (NSAID)-Sparing Effect of Secukinumab Over 16 Weeks in Patients With Ankylosing Spondylitis (ASTRUM) (NCT02763046) has completed, with no results posted. Another trial studied the efficacy and safety of SEC (NCT02896127) has results submitted and not posted. A study (NCT04156620) to demonstrate the efficacy, safety, and tolerability of an intravenous regimen of SEC compared with placebo in patients with active axial spondyloarthritis (axSpA) including AS is recruiting since December 11, 2019. A treat-to-target with SEC in axSpA Treat-to-target With Secukinumab in Axial Spondyloarthritis (TRACE) (NCT03639740) is also recruiting since January 15, 2019.

Ixekizumab in AS

Three ixekizumab (IXE) clinical trials are available on clinicaltrials.gov with 2 completed (COAST-V: NCT02696785; COAST-W: NCT02696798) (Table 1) and 1 recruiting estimated 140 Chinese participants from 25 centers (NCT04285229).

COAST-V[14] is a phase III, multicenter, randomized, double-blinded, active-control and placebo-controlled trail with a 1-year duration, followed by an optional 2-year extension study. A total of 341 patients were randomly assigned (1:1:1:1) to receive 80 mg subcutaneous IXE every 2 weeks (Q2W) or every 4 weeks (Q4W), 40 mg adalimumab Q2W, or placebo. ASAS 40 was achieved in more patients receiving IXE Q2W (43 [52%] of 83 patients) and IXE Q4W (39 [48%] of 81) compared with placebo (16 [18%] of 87) at Week 16 ($P<0.0001$ for both IXE regimens versus placebo). ASAS 20 response was achieved by 40% of patients receiving placebo at Week 16, consistent with responses reported in a recent clinical trial involving patients with AS treated by SEC (Table 1).

COAST-W[15] is a phase III randomized, double-blind, placebo-controlled trial with an inadequate response to or intolerance of 1 or 2 TNFi. A total of 316 patients were randomized in a 1:1:1 ratio to receive placebo or 80-mg subcutaneous IXE Q2W or IXE Q4W, with an 80- or 160-mg starting dose. ASAS 40 was achieved in significantly higher proportions of IXE Q2W patients ($n=30$ [30.6%]; $P=0.003$) or IXE Q4W patients ($n=29$ [25.4%]; $P=0.017$) versus the placebo group ($n=13$ [12.5%]) at Week 16. Statistically significant improvements in disease activity, function, QoL, and spinal MRI–evident inflammation were observed after 16 weeks of IXE treatment versus placebo.

At Week 16, patients receiving ixekizumab (IXE) continued their assigned treatment; patients receiving placebo (PBO) or adalimumab (ADA) were re-randomized in a 1:1 ratio to

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Table 1: ASAS 20 and ASAS 40 response rates for IL-17 inhibitors in AS and axSpA at Weeks 12 (BKZ) and 16 (SEC, IXE, and brodalumab)

Trials	ASAS 20, *n* (%)	ASAS 40, *n* (%)
SEC MEASURE 1		
SEC 150 mg SC (*n* = 125)	76 (61)	52 (42)
SEC 75 mg SC (*n* = 124)	74 (60)	41 (33)
PBO (*n* = 122)	35 (29)	16 (13)
SEC MEASURE 2		
SEC 150 mg SC (*n* = 72)	44 (61)	26 (36)
SEC 75 mg SC (*n* = 73)	30 (41)	19 (26)
PBO (*n* = 74)	21 (28)	8 (11)
SEC MEASURE 3		
SEC IV-300 mg (*n* = 76)	46 (60.5)	32 (42.1)
SEC IV-150 mg (*n* = 74)	43 (58.1)	30 (40.5)
PBO (*n* = 76)	28 (36.8)	16 (21.1)
SEC MEASURE 4		
SEC 150 mg (*n* = 116)	69 (59.5)	45 (38.8)
SEC 150 mg no load (*n* = 117)	72 (61.5)	42 (35.9)
PBO (*n* = 117)	55 (47.0)	33 (28.2)
IXE COAST-V (bDMARD-naïve AS)		
IXE Q4W (*n* = 81)	52 (64)	39 (48.1)
IXE Q2W (*n* = 83)	57 (69)	43 (51.8)
ADA Q2W (*n* = 90)	53 (59)	32 (36)
PBO (*n* = 87)	35 (40)	16 (18.6)
IXE COAST-W (TNFi-experienced AS)		
IXE Q4W (*n* = 114)	55 (48.2)	29 (25.4)
IXE Q2W (*n* = 98)	46 (46.9)	30 (30.6)
PBO (*n* = 104)	31 (29.8)	13 (12.5)
Brodalumab (axSpA)		
Brodalumab 210 mg (*n* = 80)	54 (67.5)	35 (43.8)
PBO (*n* = 79)	33 (41.8)	19 (24.1)
BKZ (AS)		
BKZ 320 mg Q4W (*n* = 61)	44 (72.1)	28 (45.9)
BKZ 160 mg Q4W (*n* = 60)	35 (58.3)	28 (46.7)
BKZ 64 mg Q4W (*n* = 61)	38 (62.3)	26 (42.6)
BKZ 16 mg Q4W (*n* = 61)	25 (41.0)	18 (29.5)
PBO Q4W (*n* = 60)	17 (28.3)	8 (13.3)

AS, ankylosing spondylitis; ADA, adalimumab; ASAS, Assessment of Spondyloarthritis International Society; axSpA, axial spondyloarthritis; bDMARD, biologic disease-modifying antirheumatic drugs BKZ, bimekizumab; COAST-V, A Study of Ixekizumab (LY2439821) in bDMARD-Naive Participants With Radiographic Axial Spondyloarthritis; COAST-W, A Study of Ixekizumab (LY2439821) in TNF Inhibitor Experienced Participants With Radiographic Axial Spondyloarthritis; PBO, placebo; SEC, secukinumab; IXE, ixekizumab; IL, interleukin; TNFi, tumor necrosis factor inhibitor.

receive IXE Q2W or IXE Q4W (PBO/IXE, ADA/IXE) through Week 52. Both IXE regimens sustained improvements in disease activity, physical function, objective markers of inflammation, quality of life (QoL), health status, and overall function up to 52 weeks.[16]

Brodalumab in axSpA

Brodalumab is a receptor antagonist of IL-17 receptor A and thus inhibits the activity of IL-17A, IL-17F, IL-17A/F, IL-17C, and IL-17E, demonstrating a potentially broader inflammation-blocking activity than selective IL-17A inhibitors. Brodalumab is approved for the treatment of plaque psoriasis in North America, Canada, Europe, Japan, and other Asian countries. A phase III study in Asia had similar ASAS 40 response rate of 43.8% with brodalumab versus 24.1% with placebo (P=0.018) and ASAS 20 response rate was 67.5% in the brodalumab group versus 41.8% in the placebo group. Treatment-emergent adverse events (AEs) were reported in 44 (55%) and 45 (57%) patients in the brodalumab and placebo groups, respectively.[17]

Bimekizumab in AS

Four studies can be found for bimekizumab (BKZ) and AS in clinicaltrials.gov with 2 active not recruiting, including 1 evaluating the long-term efficacy and safety (NCT03355573) and 1 testing the efficacy and safety of BKZ and certolizumab pegol (NCT03215277), as well as 1 suspended (study recruitment temporarily halted as a precautionary measure because of the coronavirus disease (COVID-19) pandemic) and 1 completed (NCT02963506).

In a phase IIb, randomized, double-blind, placebo-controlled, dose-ranging study,[18] a total of 303 patients were randomized in a 1:1:1:1:1 ratio to receive BKZ 16, 64, 160, or 320 mg or placebo every 4 weeks for 12 weeks (double-blind period). At Week 12, patients receiving BKZ 16 or 64 mg or placebo were re-randomized in a 1:1 ratio to receive BKZ 160 or 320 mg every 4 weeks to Week 48; other patients continued on their initial dose (dose-blind period). At Week 12, significantly more BKZ-treated patients achieved ASAS 40 compared with placebo non-responder imputation (NRI): 29.5%–46.7% versus 13.3%; P<0.05 all comparisons; odds ratio (OR) versus placebo 2.6–5.5 [95% confidence interval: 1.0–12.9]). A significant dose-response was observed (P<0.001). At Week 48, 58.6% and 62.3% of patients receiving BKZ 160 and 320 mg throughout the study achieved ASAS 40, respectively (NRI); similar ASAS 40 response rates were observed in re-randomized patients.

Safety of IL-17 inhibitors

Dyslipidemia was the most commonly reported AE in MEASURE 1 (the only 1 of the 2 MEASURE studies conducted in Taiwan, where the majority of Asian patients were enrolled).[19] However, dyslipidemia was not commonly reported in MEASURE 2. Infections, including candidiasis, were more common with SEC than with placebo during the placebo-controlled period of MEASURE 1. During the entire treatment period, pooled exposure-adjusted incidence

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rates of grade 3 or 4 neutropenia, candida infections, and Crohn's disease were 0.7, 0.9, and 0.7 cases per 100 patient-years, respectively, in SEC-treated patients. Through 2 years of MEASURE 2, across the entire treatment period (mean SEC exposure: 735.6 days), exposure-adjusted incidence rates for serious infections and infestations, Crohn's disease, malignant or unspecified tumors, and major adverse cardiac events with SEC were 1.2, 0.7, 0.5, and 0.7 per 100 patient-years, respectively. No cases of tuberculosis reactivation, opportunistic infections, or suicidal ideation were reported. The safety profile was consistent with previous reports, with no new or unexpected findings in MEASURE 3 and MEASURE 4. SEC treatment was associated with a low (<1%) incidence of immunogenicity in patients with AS.[20] The incidence rate of uveitis in SEC-treated patients with active AS does not suggest an increased risk with SEC treatment.[21]

The most common AE in IXE trials was nasopharyngitis with predominant non-Asian population enrollment. In COAST-V study, 1 serious infection occurred in each of the IXE Q2W (1%), IXE Q4W (1%), and adalimumab (1%) groups; none were reported with placebo. One (1%) candida infection occurred in the adalimumab group and 1 (1%) patient receiving IXE Q2W was adjudicated as having probable Crohn's disease. No treatment-emergent opportunistic infections, malignancies, or deaths occurred. In COAST-W study, treatment-emergent AEs were more frequent with IXE treatment than with placebo. Serious AEs were similar across treatment arms. One death was reported (IXEQ2W group). Safety through 52 weeks of IXE was consistent with safety through 16 weeks. During the double-blind period, treatment-emergent AEs occurred in 26 (43.3%) of 60 patients receiving placebo and 92 (37.9%) of 243 patients receiving BKZ, with no unexpected safety findings versus previous studies.

Conclusions

IL-17 inhibitors, including SEC, IXE, and BKZ, provide alternatives for bDMARD in AS, especially for patients with TNFi failure or intolerance, which might be safer for those at higher risk for tuberculosis. IL-17 inhibitors should be avoided in patients with AS with symptoms of inflammatory bowel disease (IBD) and uveitis. Candida infection should be carefully monitored in long-term treatment. The safety profile might be different among populations. More data on IXE and BKZ is required for further comparison of efficacy and safety between IL-17 inhibitors in AS.

Conflict of Interest

None declared.

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