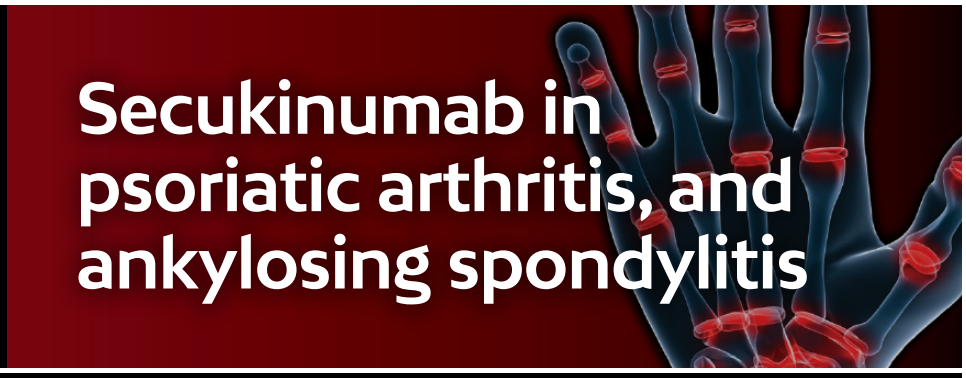
A RESEARCH REVIEW™
PRODUCT REVIEW

Secukinumab in psoriatic arthritis, and ankylosing spondylitis



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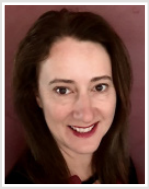
About the Expert



Julia Martin
MB ChB (Auckland); FRACP

Dr Julia Martin is a Consultant Rheumatologist at Auckland City Hospital and Honorary Clinical Senior Lecturer in Medicine, University of Auckland. She completed her fellowship in Dublin, Ireland, where her study interests included screening for latent tuberculosis prior to anti-TNF therapies in patients with inflammatory arthritis.

Dr Martin was the clinic director of Rheumatology at ADHB from 2006 to 2015 and was instrumental in establishing the biologic clinics, the infusion centre and establishing protocols for nurse led clinics. Julia is trained in point of care ultrasound in the rheumatology setting and teaches at various international meetings on this topic. She uses ultrasound routinely in patient care, from nerve blocks to steroid joint and tendon injections and more recently for the diagnosis and management of patients with vasculitis.

She has a passion for providing quality care to her patients based on best evidence and being a supervisor to training registrars.

This review discusses the evidence in support of secukinumab (Cosentyx®), a high-affinity, human, monoclonal antibody that selectively binds to interleukin-17A to inhibit its proinflammatory effects, for the management of active psoriatic arthritis (PsA), and active ankylosing spondylitis (AS), focussing on outcomes from the phase 3 studies in patients with psoriatic arthritis (FUTURE trials), and ankylosing spondylitis (MEASURE trials), as well as data from long-term follow-up of up to 5 years.

From 1 May 2021, access to secukinumab is widened to cover two rheumatological disorders, with secukinumab funded as a first-line biologic in PsA and as a second-line agent in AS. This review is sponsored by an educational grant from Novartis (NZ) Ltd.

Immune-mediated diseases

Psoriasis,[1-3] psoriatic arthritis (PsA),[4,5] and ankylosing spondylitis (AS)[6] are complex, chronic, immune-mediated, multifactorial, inflammatory diseases. PsA is characterised by peripheral arthritis, dactylitis, enthesitis, and spondylitis.[4,5] Most patients with PsA also have psoriasis, with skin disease typically preceding the manifestation of joint disease.[7] However, in some patients the skin and joint symptoms present together, and the arthritis presents first in about 10–15% of patients.[5,8] AS primarily affects the axial skeleton and is characterised by chronic back pain, sacroiliitis, enthesitis, and the propensity for sacroiliac joint and spinal fusion.[6]

These immune mediated diseases are associated with a number of comorbidities.[8,9] PsA may occur in up to 30% of patients with psoriasis, and can lead to progressive joint damage due to cartilage degradation, bone resorption, and osteo-proliferation.[8] Other comorbidities that occur in patients with either plaque psoriasis or PsA include cardiovascular disease, metabolic disease, obesity, inflammatory bowel disease, and mood disorders (e.g. depression, anxiety, and suicidal ideation).[10]

Given the signs and symptoms of the disease, as well as the potential burden of the comorbidities, psoriasis, PsA, and AS can have an adverse impact on the patient's personal and professional relationships, social interactions, physical functioning (particularly PsA and AS), and health-related quality of life (HR-QoL).[3,11-15]

A growing understanding of the immune-pathophysiology of psoriasis, PsA, and AS has led to the identification of new drug targets and the development of agents with novel mechanisms of action. In particular, secukinumab (Cosentyx®), a high-affinity, human, monoclonal antibody, selectively binds to and neutralises the pro-inflammatory cytokine interleukin-17A (IL-17A).[16-20] IL-17A is produced by a subset of T helper cells (Th17) as well as other T cells, neutrophils, and mast cells, and it promotes the expression of other pro-inflammatory cytokines as well as effector proteins.[21] This cascade results in the activation of neutrophils and macrophages as well as epithelial cells and fibroblasts, and is considered to play an important role in the pathophysiology of plaque psoriasis, PsA, and AS.[17-21] Elevated levels of IL-17A are found in psoriatic plaques and in the peripheral blood of patients with psoriatic disease.[22,23] Increased numbers of IL-17A-producing cells are also found in the circulation and joints of patients with PsA and AS.[24]

Focus on secukinumab

Secukinumab is indicated for the treatment of adult patients with:[16]

- Moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy;
- Active PsA when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate; and
- Active AS.

Mechanism of action

Secukinumab is a fully human human immunoglobulin G1 (lgG1) anti-IL-17A monoclonal antibody that acts by selectively binding and neutralizing IL-17A, thus inhibiting its interaction with IL-17 receptors.[16,20] As a result, secukinumab inhibits the release of pro-inflammatory cytokines, chemokines, and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases.[16,20]

Dosage and administration

Psoriatic arthritis and ankylosing spondylitis: In patients with PsA or AS, the recommended dose is 150 mg by subcutaneous injection, with initial dosing at weeks 0, 1, 2, 3, and 4, and then followed by the same dose every month.[16] The dose can be increased to 300 mg (given as two subcutaneous injections).[16]

In patients with PsA who are inadequate responders to anti-tumour necrosis (TNF)-alpha therapy, or in patients with concomitant moderate-to-severe plaque psoriasis, the recommended dose is 300 mg (given as two subcutaneous injections of 150 mg) with initial dosing at weeks 0, 1, 2, 3, and 4, and followed by the same dose every month. Secukinumab may be administered with or without methotrexate.[16]

Contraindications

Cosentyx is contraindicated in patients with severe hypersensitivity reactions to the active substance or any of the excipients.[16] Secukinumab is contraindicated in patients with clinically important, active infections.[16]

Vaccinations

Live vaccines should not be given concurrently with secukinumab.[16]

IL-17 inhibitors do not appear to increase the risk of herpes zoster infections.[25] Nevertheless, herpes zoster vaccination should be considered on a case-by-case basis prior to initiating IL-17 inhibitor therapy.[25]

Pregnancy

There are no adequate data regarding the use of secukinumab in pregnant women.[16,26] Secukinumab should be used in pregnancy only if the benefits clearly outweigh the potential risks.[16]

Pharmacokinetic profile

The pharmacokinetic profile of secukinumab is similar when administered to patients with plaque psoriasis, PsA, or AS.[16] Secukinumab's pharmacokinetic profile is typical of a fully human immunoglobulin (Ig) G1 molecule with slow subcutaneous absorption, slow clearance, and a long half-life.[16,20,27]

Studies in patients with psoriasis indicate that exposure to secukinumab was dose proportional.[16] Peak concentrations were reached approximately 6 days after a single subcutaneous injection, and steady state was reached after 20 weeks with monthly dosing. The volume of distribution following a single intravenous administration to patients with plaque psoriasis was low (7.10 to 8.60 L), suggesting limited distribution to peripheral compartments. Mean systemic clearance was 0.19 L/day, and the mean elimination half-life was estimated to be 27 days.[1] The bioavailability of secukinumab was 73%.[1] It is thought secukinumab is metabolised to small peptides via catabolic pathways in a manner similar to endogenous IgG.[1]

Given the large molecular size (~150 kDa) of secukinumab, and because intact immunoglobulin is filtered by the kidney to a limited extent, only very small amounts of secukinumab are expected to be excreted in the urine.[27] Thus, renal impairment is not likely to influence urinary excretion and the overall pharmacokinetic profile of secukinumab.

Hepatic impairment is not be expected to influence metabolism or excretion of secukinumab.[27] However, no pharmacokinetic data are available in patients with renal impairment or hepatic impairment.[1]

Interaction profile

The formation of some cytochrome CYP450 enzymes is suppressed by increased levels of cytokines during chronic inflammation.[20] Potentially, secukinumab may increase/restore the expression level of CYP3A4 (a prominent CYP450 enzyme), and consequently decrease the exposure to concomitant medications that are metabolised by CYP3A4.[20,28] However, no clinically relevant pharmacokinetic interaction was observed between secukinumab and midazolam (a CYP3A4 substrate).[28] Nevertheless, it is recommended that in patients treated with secukinumab and concomitant CYP450 substrates, particularly those with a narrow therapeutic index, that monitoring for therapeutic effect or drug concentration should occur and dosage adjustment be made as needed.[1]

Key trials in patients with psoriatic arthritis

FUTURE trials

The safety and efficacy of secukinumab in patients with active PsA were investigated in five multicentre, randomised, double-blind, placebo-controlled phase 3 studies (FUTURE 1,[29-32] a 2-year study with a 3-year extension; FUTURE 2,[33-35] a 5-year study; FUTURE 3,[36] a 3-year study; FUTURE 4,[37] a 2-year study and FUTURE 5,[38,39] a 2-year study).

Patients included in the trials were aged ≥18 years and had a diagnosis of PsA that met the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria of ≥3 swollen and ≥3 tender joints, despite previous treatment with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or DMARDs.[29-39] Key exclusion criteria included active/history of ongoing infection, prior use of a biologic other than an anti-TNF agent, and active inflammatory disease other than PsA.[29-39]

The primary endpoint in these studies was the percentage of patients with ≥20% improvement in the American College of Rheumatology (ACR 20) criteria at week 24 (FUTURE 1, 2, 3) or week 16 (FUTURE 4, 5).[29-39]

In these studies, secukinumab was administered with or without a loading regimen, followed by a subcutaneous maintenance regimen (**Figure 1**).[29-39] In FUTURE 1, secukinumab was administered as an intravenous loading dose of 10 mg/kg at weeks 0, 2, and 4.[29-32] In the other trials, secukinumab was administered as a subcutaneous loading dose of 75 mg (non-approved dose; FUTURE 1 and 2), 150 mg (FUTURE 1, 2, 3, 4, and 5) or 300 mg (FUTURE 3) at weeks 0, 1, 2, 3, and 4.[29-32] In both the FUTURE 4 and 5 trials, one of the secukinumab 150 mg maintenance treatment arms did not received a loading regimen.[37-39] Outcomes from these treatment arms will not be presented in this review, and only outcomes from treatment arms using the approved maintenance dosage will be reviewed. The secukinumab maintenance regimen consisted of 75 mg (non-approved dose; FUTURE 1 and 2), or 150 or 300 mg every 4 weeks (FUTURE 1, 2, 3, 4, 5; **Figure 1**).[29-39] Patients initially randomised to placebo were re-randomised to subcutaneous secukinumab according to response; at week 16 for non-responders, or week 24 for responders (i.e. patients who achieved ACR 20).[29-39] The FUTURE 3 trial involved self-administration of secukinumab using an auto-injector.[36]

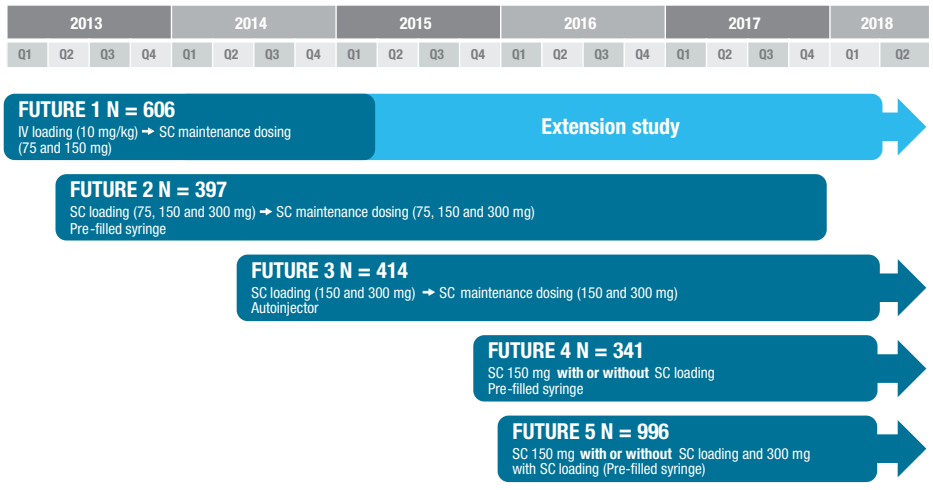


Figure 1. The FUTURE clinical trials which assessed secukinumab in patients with PsA

IV, intravenous; SC, subcutaneous.

The FUTURE studies contained a mixed population of anti-TNF-naïve and anti-TNF-inadequate responders (**Table 1**), and patients who were, or were not, receiving concomitant methotrexate (**Table 1**).[29-39] At baseline, approximately half of the patients had at least 3% body surface area involvement with skin psoriasis.[16] Less than half of the patients reported dactylitis and over half reported enthesitis (**Table 1**).[29-39]

Table 1. Patient characteristics in the FUTURE trials in patients with active psoriatic arthritis[29-39]

	FUTURE 1 [29-32] (N=606)	FUTURE 2 [33-35] (N=397)	FUTURE 3 [36] (N=414)	FUTURE 4 [37] (N=341)	FUTURE 5 [38,39] (N=996)
Treated with concomitant MTX, % pts	61	47	48	≈50	50
Anti-TNF-naïve, % pts	71	65	68.1	76	70
Psoriasis affecting ≥3% of BSA, % pts	54	41-58	43-49	47-54	52
Dactylitis, % pts	54	28-46	26-33	34-39	39
Enthesitis, % pts	61	56-69	63-72	58-67	60

BSA, body surface area; MTX, methotrexate; TNF, tumour necrosis factor.

Signs and symptoms

In patients with PsA, secukinumab, compared with placebo, resulted in significant improvement in measures of disease activity in the short term (weeks 16 and 24) in the FUTURE trials (**Table 2**), with the benefits maintained over the long term (up to 5 years) with secukinumab maintenance treatment.[29-39]

ACR 20: All trials achieved the primary endpoint of ACR 20 responses, with a significantly greater response with secukinumab 150 or 300 mg than with placebo (**Table 2**).[29-39]

The onset of action of secukinumab occurred as early as week 2, as demonstrated in FUTURE 2 (**Figure 2**).[16,35]

With long-term treatment (up to 5 years), ACR 20 responses achieved in the short-term with secukinumab 150 or 300 mg were sustained or increased across the FUTURE trials.[29-39] For example, in FUTURE 2, ACR 20 responses reported at 24 weeks (51% and 54%) increase to 73.8% and 79.2% at 5 years in patients who were originally randomised to secukinumab 150 or 300 mg (**Figure 2**).[35] Similar outcomes were reported in recipients of secukinumab 150 mg in FUTURE 1;[31] with 81.8%% (193 of 236) patients treated with secukinumab 150 mg completing 5 years of treatment, ACR20 responses increased from 50.0% at 24 weeks to 67.9% at 5 years.[31]

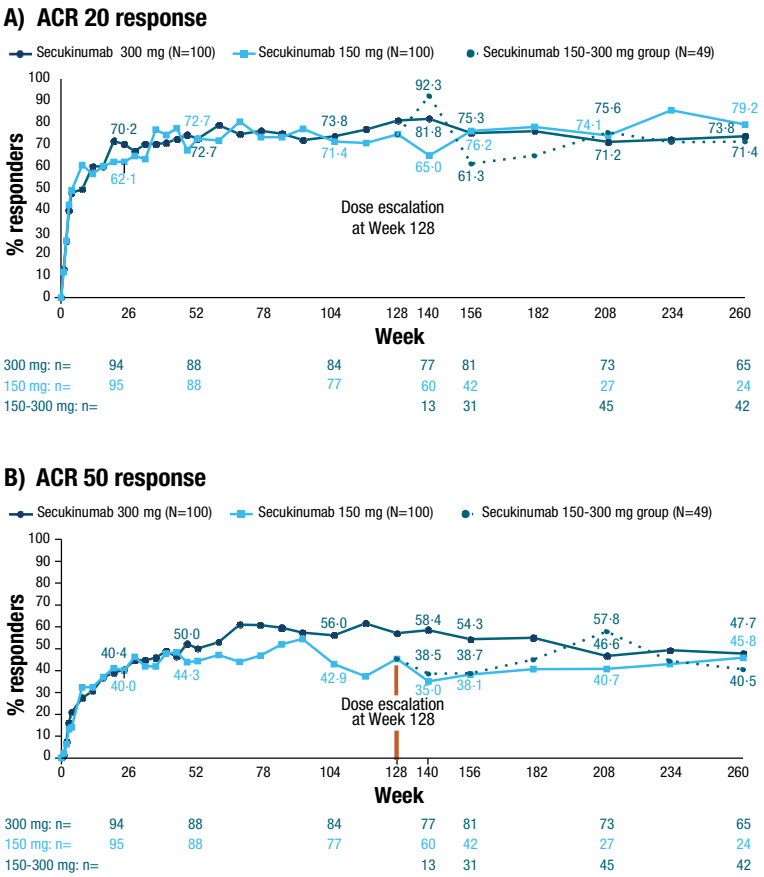


Figure 2. Percentage of patients with:
A) ≥20% improvement in the American College of Rheumatology (ACR 20) criteria and
B) ≥50% improvement in ACR (ACR 50) over 5 years in patients with psoriatic arthritis in the FUTURE 2 trial[35]

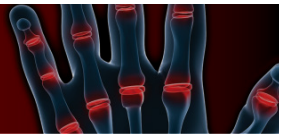
ACR 50 responses: ACR 50 responses achieved in the short-term (weeks 16 or 24: **Table 2**) were maintained or increased with long-term treatment.[29-39] For example, in FUTURE 2, patients originally randomised to secukinumab 300 mg and 150 mg achieved ACR 50 responses at 24 weeks of 35% and 35%, respectively, with these responses increasing to 47·7% and 45·8% at 5 years (**Figure 2B**). Similarly in FUTURE 1, ACR 50 responses increased from 34.7% at 24 weeks to 52.7% at 5 years in patients originally randomised to secukinumab 150 mg.[31]

PASI responses: Across the FUTURE studies, PASI 75 and PASI 90 responses were generally significantly higher with secukinumab 300 mg and 150 mg compared with placebo in the short term (16 or 24 weeks; **Table 2**), with these responses being maintained over the long term.[29-39]

Resolution of dactylitis and enthesitis: Dactylitis and enthesitis was present in many PsA patients at baseline in the FUTURE trials (**Table 1**). In the short term (16 or 24 weeks), secukinumab 150 or 300 mg was associated with a resolution of dactylitis in 33-66% of evaluable patients and resolution of enthesitis in 32-56% of patients (**Table 2**).[29-39] These rates were maintained or improved with long-term treatment. For example, in FUTURE 2, treatment with secukinumab 300 or 150 mg was associated with the majority of evaluable patients achieving complete resolution of dactylitis at week 24 (56.5% and 50.0%),[16] with these rates being maintained in the long term (86.3% and 83.9% at year 3,[35] 88.9% and 90% at year 4,[35] and 87.5% and 82.1% at year 5[35]). Respective rates for the resolution of enthesitis in FUTURE 2 were 48.2% and 42.2% at 24 week,[16] 68.7% and 65% at year 3,[35] 69.5% and 70.4% at year 4,[35] and 76.5 and 75.5% at year 5.[35]

Concomitant methotrexate therapy: Similar responses for primary and key secondary endpoints were seen in PsA patients regardless of whether or not they were receiving concomitant methotrexate therapy.[16]

Anti-TNF therapy: The FUTURE studies contained a mixed population of anti-TNF-naïve and anti-TNF-inadequate responders (**Table 1**).[29-39] Secukinumab, compared with placebo, improved the signs and symptoms of PsA irrespective of prior anti-TNF treatment. However, ACR 20/50 and PASI response rates were generally numerically higher in patients who were anti-TNF-naïve. For example, in FUTURE 2, ACR 20 response at week 24 was achieved by 63% and 58% of anti-TNF-naïve patients treated with secukinumab 150 and 300 mg versus 16% of placebo recipients (both p<0.0001); an ACR 20 response at week 24 was achieved by 30% and 45% of anti-TNF-inadequate responders treated with secukinumab 150 and 300 mg compared with 14% of placebo recipients, with the response in the secukinumab 300 mg group being significantly higher than with placebo (p=0.0077).[34] Improvements in both ACR 20 and 50 responses were sustained at 5 years in both anti-TNF-naïve and anti-TNF-inadequate responder patients, although responses were generally higher in the anti-TNF-naïve patients.[35]



Physical function and health related quality of life

In the FUTURE studies,[29-39] patients treated with secukinumab 150 mg and 300 mg, compared with placebo, reported improvements in physical function as assessed by change from baseline in Heath Assessment Questionnaire-Disability Index (HAQ-DI) at week 16 or 24 (**Table 2**), with these improvements sustained in the long term (up to 5 years in FUTURE 1[31] and 2[35]).

Significant improvements in HR-QoL, as measured by the Short Form (36) Health Survey Physical Component Summary (SF-36 PCS) score (**Table 2**), were also reported at week 16 or 24, and in the long-term in the FUTURE 1-4 studies.[29-37]

Use of auto-injector

FUTURE 3 demonstrated the acceptability of administering secukinumab using an auto-injector device.[36] More than 90% of total patients reported no pain and reaction during or after the injection, and ≥88% were either satisfied or very satisfied with the use of the auto-injector device and found it easy or very easy to use.[36]

Radiographic response

Secukinumab 150 mg and 300 mg, compared with placebo, significantly inhibited radiographic progression of PsA at week 24 in FUTURE 1 and in FUTURE 5, as assessed by the modified Total Sharp Score (mTSS; **Table 3**), and this effect was maintained in the long term.[38]

In FUTURE 1, no radiographic progression (change from baseline in mTSS ≤0.5) occurred in 82.3% of patients in the secukinumab 150 mg group and 75.7% in placebo group at week 24. With continued secukinumab 150 mg therapy, no radiographic progression was reported in 85.7% of evaluable patients at 1 year,[32] and 78.1%[30] at 3 years. In FUTURE 5, no radiographic progression occurred in 88.0%, 79.8%, and 73.6% of evaluable patients treated with secukinumab 300 mg, 150 mg, and placebo, respectively, at week 24.[38] With continued secukinumab 300 mg and 150 mg therapy, no radiographic progression occurred in 91.8% and 85.2% of evaluable patients, respectively, at 1 year[39] and 89.5% and 82.3% evaluable patients, respectively, at 2 years.[44]

Table 2. Outcomes from the phase 3 FUTURE trials at week 16 (FUTURE 4 or 5) or week 24 (FUTURE 1, 2, 3) in patients with psoriatic arthritis. Only data from treatment arms receiving approved maintenance dosages, with an associated loading regimen, are shown.

Outcome	FUTURE 1 [29-32] (week 24)		FUTURE 2 [33-35] (week 24)			FUTURE 3 [36] (week 24)			FUTURE 4 [37] (week 16)		FUTURE 5 [38,39] (week 16)		
	Sec 150 (n=202)	Placebo (n=202)	Sec 150 (n=100)	Sec 300 (n=100)	Placebo (n=98)	Sec 150 (n=138)	Sec 300 (n=139)	Placebo (n=137)	Sec 150 (n=114)	Placebo (n=114)	SEC 150 (n=220)	SEC 300 (n=222)	Placebo (n=332)
ACR 20 response[a], % pts	50.0***	17.3	51.0***	54.0***	15.3	42.0***	48.2***	16.1	41.2***	18.4	55.5***	62.6***	27.4
ACR 50 response, % pts	34.7***	7.4	35.0	35.0**	7.1%	18.8*	34.5***	8.8	22.8**	6.7	35.9*	39.6*	8.7
PASI 75, % pts	61.1***	8.3	48.3**	63.4***	16.3	50.0*	46.8*	10.2	52.7***	8.1	60.0*	70.0*	12.3
PASI 90, % pts	45.4***	3.7	32.8**	48.8***	9.6	36.8	33.9	6.8	36.4***	1.6	36.8*	53.6*	9.3
DAS28-CRP score, LS mean changes from BL[b]	-1.62***	-0.77	-1.58**	-1.61***	-0.96	-1.24*	-1.56***	-0.64	-0.98***	-0.21	-1.29*	-1.49*	-0.63
HAQ-DI, mean change from BL[c]	-0.40***	-0.17	-0.48	-0.56**	-0.31	–0.27	–0.38	–0.17	NR	NR	-0.44***	-0.55***	-0.21
SF36-PCS, mean change from BL[d]	+5.91***	+1.82	+6.39**	+7.25**	+1.95	+3.42	+6.46**	+2.94	+3.42**	+0.63	NR	NR	NR
Dactylitis resolution, % pts	52.4*[b]	15.5	50.0	56.5	14.8	38.9	47.8**	13.9	32.5	31.8	57.5*	65.9*	32.3
Enthesitis resolution, % pts	47.5*[b]	12.8	42.2	48.2	21.5	36.8	39.8**	15.3	32.4	21.1	54.6*	55.7*	35.4

*p<0.05, **p<0.01, ***p<0.001 vs PL.

ACR 20, 20% improvement in American College of Rheumatology criteria; BL, baseline; DAS28-CPR, 28-joint Disease Activity Score using C-Reactive Protein; HAQ-DI, Health Assessment Questionnaire Disability Index (HAQ-DI) LS, least squares; PASI 75/90, improvement of ≥75%/90% in the Psoriasis Area-and-Severity Index; pts, patients Sec, secukinumab.

[a]Primary endpoint. The ACR uses seven measures of disease activity to help evaluate improvement. These measures include swollen joint count, tender joint count, patient pain assessment, patient global assessment, physician global assessment, disability index, and C-reactive protein.[40]

[b]A change of -1.0 points is considered to be a minimum clinically important difference (MCID).[41]

[c]A change of -0.35 points is considered to be a MCID.[42]

[d]A change of 2.5–5.0 points is considered to be a MCID.[43]

Table 3. Change in modified Total Sharp Score in psoriatic arthritis in FUTURE 1 and FUTURE 5 studies

Mean change in modified Total Sharp Score from baseline	FUTURE 1 [30,32]		FUTURE 5 [38,39]		
	Secukinumab 150 mg	Placebo	Secukinumab 300 mg	Secukinumab 150 mg	Placebo
Baseline	22.3	28.4	12.9	13.6	15.0
Week 24	n=185	n=179	n=217	n=213	n=296
	0.13*	0.57	0.02*	0.13*	0.5

*p<0.05 vs placebo.

MAXIMISE

MAXIMISE is a randomised, double-blind, placebo-controlled, multicentre, 52-week study in 495 patients with active PsA (CASPAR criteria) and axial skeleton involvement (defined by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4, spinal pain visual analogue scale (VAS) ≥40 [0 to 100 mm scale]) who had inadequate response to at least two NSAIDs for at least 4 weeks.[45,46] Patients were randomised to receive subcutaneous secukinumab 150 mg, 300 mg or placebo at weeks 0, 1, 2, 3, and 4, then every 4 weeks thereafter. At week 12, patients treated with placebo were re-randomised to secukinumab 300 or 150 mg.

Secukinumab 300 and 150 mg provided rapid and significant improvement, compared with placebo, when assessed according to Assessment of Spondylo Arthritis international Society criteria (ASAS) 20 responses (primary endpoint) at week 12 (63.1% and 66.3% vs 31.3%; p<0.0001).[45,46] These responses were maintained and improved after 52 weeks of secukinumab treatment, with ASAS 20 responses of 81.3% with continued secukinumab 300 mg and 80.1% with continued secukinumab 150 mg.[46]

EXCEED

The EXCEED study provides comparative evidence on two biological agents with different action mechanisms in the management of PsA.[47]

EXCEED was a parallel-group, double-blind, active-controlled, phase 3b, multicentre trial in patients with active PsA.[47] Eligible patients met the CASPAR criteria of PsA (≥3 swollen and ≥3 tender joints) despite previous treatment with NSAIDs, corticosteroids, or DMARDs, had active plaque psoriasis with at least one plaque of at least 2 cm diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis, and were naïve to treatment with biologicals.[47] Eligible patients (n=853) were randomised to secukinumab (n=426) or adalimumab (n=427).[47] Subcutaneous secukinumab 300 mg was administered as a pre-filled syringe at week 0, 1, 2, 3, and 4 and then every 4 weeks thereafter until week 48. A subcutaneous injection of adalimumab 40 mg was administered every 2 weeks from week 0 until week 50.

A total of 709 (83%) patients completed week 52 of the study.[47] The primary endpoint of superiority of secukinumab compared with adalimumab for ACR20 response at week 52 was not met, with an ACR 20 response in 67% of secukinumab recipients compared with 62% of adalimumab recipients (odds ratio 1·30, 95% CI 0·98, 1·72; p=0·0719). However, secukinumab was associated with a higher treatment retention rate than adalimumab, with 14% of secukinumab recipients and 24% of adalimumab recipients discontinuing treatment by week 52.[47] The statistical analysis was via a hierarchical model meaning that once the primary endpoint was not considered significant, secondary endpoints (such as the resolution of dactylitis, or resolution of enthesitis) were not formally tested for statistical significance.

Expert's comments

Overall, secukinumab is a welcome addition to the Rheumatologist's armamentarium for PsA treatment in New Zealand.

Until recently only our PsA patients who made the dermatology special authority criteria were able to gain access. These patients were usually placed on the 300 mg dose. Patients who managed to get it prescribed in this manner invariably did well from their PsA perspective, with the only significant side effect that I have encountered being mild fungal skin infections.

Given that concomitant methotrexate has not proven beneficial, the Rheumatologist is then left with the decision of whether or not to stop this agent (if they are on it.) Given the data to date, this would seem a reasonable step to take.

The recent Pharmac announcement of widening access to secukinumab to PsA patients as a first-line biologic agent, at a dose no greater than 300 mg monthly, is a very welcome development.

As welcome as this news is however, there is still a gap in the NZ Rheumatologists' ability to adequately treat PsA. In particular, those patients who suffer predominantly from enthesial disease and/or dactylitis are not specifically mentioned in the new PHARMAC guidelines. In the longer term, it would be ideal if these patients were also PHARMAC funded.

Key trials in patients with ankylosing spondylitis

MEASURE trials

The efficacy of subcutaneous secukinumab for the treatment of AS was assessed in randomised, double-blind, placebo-controlled phase 3 trials (MEASURE 1,[48-50] a 2-year study with a 3-year extension; MEASURE 2,[48,51,52] a 5-year study; MEASURE 3,[53] a 3-year study; and MEASURE 4,[54] a 2-year study; **Figure 3**).

Patients included in the MEASURE trials were aged ≥18 years with active AS (according to the modified New York criteria), a BASDAI score ≥4, and a spinal pain score of ≥4 cm on a 10 cm VAS, despite treatment with the maximum tolerated doses of NSAIDs.[48-54]

In MEASURE 1 and 3,[48,49,53] secukinumab recipients received intravenous loading doses of secukinumab 10 mg/kg at weeks 0, 2, and 4. In MEASURE 2,[48,51] secukinumab was administered as a subcutaneous loading dose of 75 or 150 mg at weeks 0, 1, 2, 3, and 4. In MEASURE 4,[54] subcutaneous secukinumab was self-administered with, or without a loading regimen (i.e. 150 mg at weeks 0, 1, 2, 3, and 4). In all MEASURE studies, loading doses were followed by maintenance therapy of subcutaneous secukinumab 75 or 150 mg (MEASURE 1 and 2), secukinumab 150 or 300 mg (MEASURE 3), or secukinumab 150 mg (MEASURE 4) every 4 weeks thereafter.[48-54]

In MEASURE 1, patients initially randomised to placebo were re-randomised to subcutaneous secukinumab 75 or 150 mg according to response; at week 16 for non-responders, or week 24 for responders.[48,49] In the other MEASURE trials, placebo recipients were re-randomised to receive secukinumab 75 or 150 mg (MEASURE 2),[48,51] or 150 or 300 mg (MEASURE 3) from week 16.[53] In MEASURE 4, all placebo recipients were switched to open-label secukinumab 150 mg at week 16.[54]

Across all MEASURE trials, the primary end point was the percentage of patients who achieved ASAS 20 response at week 16.[48-54]

This section will focus on only outcomes in patients receiving the approved secukinumab dosing regimen.

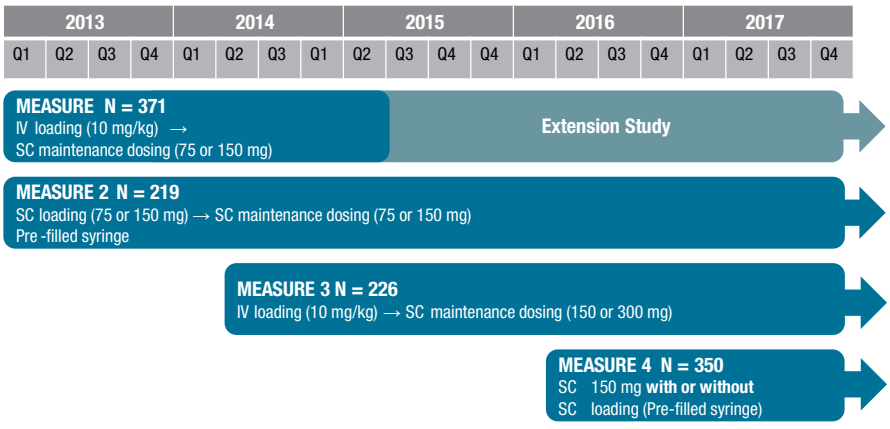


Figure 3. The MEASURE clinical trials which assessed secukinumab in patients with ankylosing spondylitis.

IV, intravenous; SC, subcutaneous.

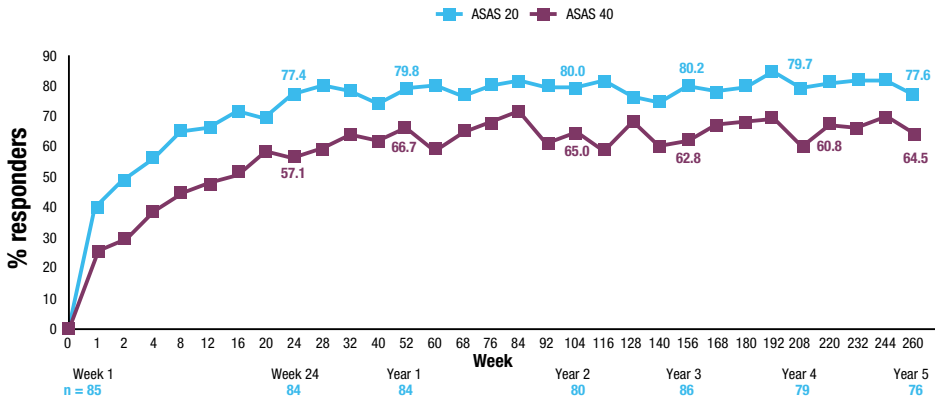


Figure 4. ASAS 20/40 response rates through 5 years in secukinumab 150 group in patients originally randomised to secukinumab 150 mg only (MEASURE 1 trial).

Data from placebo switchers or patients whose dose was escalated are not included. ASAS, Assessment of SpondyloArthritis international Society

Signs and symptoms

In MEASURE 1, 2, and 3, subcutaneous secukinumab 150 or 300 mg improved the signs and symptoms of AS (**Table 4**), with significantly more secukinumab than placebo recipients achieving an ASAS 20 response at week 16.

These efficacy endpoint was maintained with long-term maintenance therapy, with data to 5 years available for MEASURE 1[50] and MEASURE 2.[52] In MEASURE 1, of the patients who remained in the study who had originally been randomised to secukinumab 150 mg, ASAS 20/40 responses were 77.6% and 64.6%, respectively (**Figure 4**).[50] In MEASURE 2, ASAS 20/40 responses at 5 years occurred in 67% and 50% of evaluable patients, respectively, treated with secukinumab 150 mg.

Improvements were maintained regardless of prior exposure to anti–TNF therapy, although responses tended to be greater responses in anti–TNF-naïve patients.

Physical function and HR-QoL

In the MEASURE studies, treatment with secukinumab 150 mg was associated with improvements in HR-QoL improvements, as assessed by the Ankylosing Spondylitis Quality of Life scale (ASQoL) and SF-36 PCS, in the short-term (16 weeks; **Table 4**), with these improvements being sustained with longer-term treatment.[48-54]

Expert's comments

All Rheumatologists across New Zealand will welcome this agent to aid treatment in TNF-refractory AS. These patients invariably end up tied to hospital infusion centres for infliximab after the failure of adalimumab and etanercept. However, there are some patients that, despite shortening the intervals between infliximab infusions, fail to respond adequately or lose response with time.

The PHARMAC decision to extend funding of secukinumab at 150 mg SC monthly, as a second-line biologic after adalimumab and/ or etanercept is a welcome development.

For those patients with scaroillitis and coexistent peripheral manifestations, such as enthesial disease, dactylitis, or even some skin disease, secukinumab should probably be our first-line choice. However, as mentioned , this patient cohort is unfortunately not addressed with the recent funding decision due to the lack of inclusion of dactylitis and enthesial disease in special authority criteria in this spectrum of disorders.

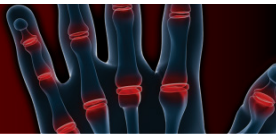
Table 4. Outcomes from the phase 3 MEASURE trials at week 16 in patients with ankylosing spondylitis showing secukinumab data of approved dosage regimens only (i.e. treatment arms involving a loading regimen and maintenance dosing of 150 mg)

Outcome	MEASURE 1 [53]		MEASURE 2 [53]		MEASURE 3 [53]			MEASURE 4 [54]	
	Sec 150 (n=125)	Placebo (n=122)	Sec 150 (n=72)	Placebo (n=74)	Sec 150 (n=74)	Sec 300 (n=76)	Placebo (n=76)	Sec 150 (n=116)	Placebo (n=62)
ASAS 20 response,[a] % pts	61***	29	61***	28	58*	61**	37	60	47
ASAS 40 response, % pts	42***	13	36***	11	41*	42*	21	39	28
ASAS 5/6 response, % pts	49***	13	43***	8	42*	40*	15	37	29
ASAS partial remission, % pts	15***	3	14	4	10	21*	3		
hsCRP, post-baseline/baseline ratio	0.40***	0.97	0.55***	1.13	0.55*	0.48*	1.09	0.59	1.12
BASDAI, mean change from baseline score	-2.32***	-0.59	-2.19***	-0.85	-2.3*	-2.7*	-1.5	-2.39	-1.86
ASQoL, mean change from baseline score	-3.58***	-1.04	-4.00**	-1.37				-3.79	-2.84
SF-36 PCS, mean change from baseline score	+5.57***	+0.96	+6.06***	+1.92				+5.90	+4.50

ASAS, Assessment of SpondyloArthritis international Society; ASQoL Ankylosing Spondylitis Quality of Life score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index, hsCRP, high-sensitivity C-reactive protein; pts patients, Sec, secukinumab; SF-36 PCS, 36-item Short-Form Health Survey physical component summary.

*p<0.05, **p<0.01, ***p<0.001 vs placebo

[a]Primary endpoint.



Safety profile of secukinumab

As well as safety outcomes being reported in the individual phase 3 trials across all three indications, an integrated analysis of safety data from 21 clinical trials involving secukinumab in plaque psoriasis, PsA and AS has been conducted.[16,55] The pooled safety analyses included 7355 secukinumab-treated patients with an overall exposure of 16,226.9 patient-years.[55]

Adverse events were reported as exposure-adjusted incident rates (EAIRs) per 100 patient-years.

Secukinumab was generally well tolerated in the placebo-controlled phase 3 trials, with its tolerability profile consistent across these indications.[16,55] Most adverse events were mild to moderate infections, such as upper respiratory tract infections (most frequently nasopharyngitis, rhinitis), oral herpes, or fungal infections (e.g. candidiasis, or tinea pedis).[16,55] Headache and diarrhoea were also commonly reported.[16,55] No new safety signals were reported with long-term secukinumab treatment.[16,55]

Infections: Given its mechanism of action, secukinumab has the potential to increase the risk of infections.[16] However, most infections were mild to moderate across all three approved indications in clinical trials.[16] In the placebo-controlled period of plaque psoriasis clinical trials (involving 1,382 patients treated with secukinumab and 694 patients treated with placebo for up to 12 weeks), infections were reported in 28.7 % of secukinumab compared with 18.9 % of placebo recipients, with serious infections occurring in 0.14 % secukinumab recipients and 0.3 % of placebo recipients.[16] Similar infection rates were reported in psoriatic arthritis and ankylosing spondylitis clinical studies.[16] Exposure-adjusted incident rates (EAIRs) per 100 patient years for serious infections are presented in **Table 5**.[55]

The incidence of mucosal or cutaneous candida infections was increased with secukinumab, compared with placebo, treatment.[16,55] Most cases of candida infection were mild or moderate in severity, self-limited, or responsive to standard treatment, and did not lead to secukinumab discontinuation.[16,55] EAIRs per 100 patient-years across the trials for candida infection were low (**Table 5**).[55]

Neutropenia: Across the phase 3 clinical studies, neutropenia occurred more frequently with secukinumab than with placebo, with a similar incidence across the three indications (see **Table 5** for EAIRs).[16,55] Most cases were mild, transient, and reversible.[16,55]

Major adverse cardiovascular events (MACE): MACE events have been reported in secukinumab across the clinical trials, but the EAIRs are low (**Table 5**).[16,55]

Inflammatory bowel disease (IBD): Exacerbations or the development of new cases of inflammatory bowel disease (IBD) have been reported in patients receiving secukinumab, including some serious cases (see **Table 5** for EAIRS).[16,55] Caution is advised when prescribing secukinumab to patients with IBD.[16,55]

Table 5. Exposure-adjusted incident rates (EAIRs) in patients treated with secukinumab in the clinical trials (pooled analysis)[16,55]

Adverse event	EAIR per 100 patient years		
	Plaque psoriasis (N=5181)	Psoriatic arthritis (N=1380)	Ankylosing spondylitis (N=794)
Serious infections	1.4	1.9	1.2
Candida infections	2.2	1.5	0.7
MACE	0.3	0.4	0.6
Neutropenia	0.3	0.2	0.5
IBD	0.01	0.05	0.1
Crohn's disease	0.05	0.08	0.4
Ulcerative colitis	0.1	0.08	0.2

EXPERT'S CONCLUDING REMARKS

Overall, IL-17 inhibition is a key mechanism to block activity in psoriasis, PsA and AS. Access to secukinumab in New Zealand was unequitable across disciplines and needed to change.

The new PHARMAC funding changes are a giant leap forward from our current options. It does not however address all the concerns that we have for our PsA and AS patients. We will also have to agitate for a different mechanism of action for our patients with co-existing inflammatory bowel disease.

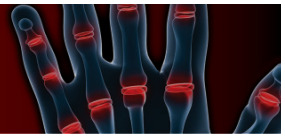
TAKE HOME MESSAGES

- Secukinumab (Cosentyx®) is a fully human monoclonal antibody against interleukin-17A which is approved for the treatment of moderate-to-severe plaque psoriasis, active PsA, and active AS
- Secukinumab improves the signs and symptoms of these immune-mediated disease, including both articular, axial, and cutaneous disease manifestations, with secukinumab also being associated with improvements in dactylitis and enthesitis
- Secukinumab is associated with improvements in patient-reported physical functioning and HR-QoL across these indications
- The onset of action of secukinumab is generally within the first 2-3 weeks of initiation of treatment
- Long-term administration (up to 5 years) with once-monthly maintenance dosing effectively maintains the improvements in the signs and symptoms gained in the short term
- Secukinumab is generally well tolerated, with its tolerability profile being consistent across the three approved indications. Most adverse events were mild to moderate infections, such as upper respiratory tract infections (most frequently nasopharyngitis, rhinitis) or fungal infections
- Caution is required when prescribing secukinumab to IBD patients
- Secukinumab is now funded under Special Authority as a first-line biologic for PsA and as a second-line biologic for AS

RESOURCES

DermNet NZ is an excellent resource with information on psoriatic arthritis and ankylosing spondylitis: http://www.dermnetnz.org.
Links to a downloadable PASI form and calculator: http://pasi.corti.li/
Screening tool for psoriatic arthritis: https://www.psoriasis.org/sites/default/files/screening_tool_for_psoriatic_arthritis.pdf

Secukinumab in psoriatic arthritis, and ankylosing spondylitis



Special Authority for Subsidy

Cosentyx® (secukinumab) is fully funded in New Zealand by special authority.
Please refer to www.pharmac.govt.nz for the full criteria for initial applications and renewals before prescribing.

INITIAL APPLICATION - psoriatic arthritis
Applications only from a rheumatologist. Approvals valid for 6 months.

Prerequisites (tick boxes where appropriate)

☐ The patient has had an initial Special Authority approval for adalimumab or etanercept for psoriatic arthritis

and

☐ The patient has experienced intolerable side effects from adalimumab or etanercept

or

☐ The patient has received insufficient benefit from adalimumab or etanercept to meet the renewal criteria for adalimumab or etanercept for psoriatic arthritis

or

☐ Patient has had severe active psoriatic arthritis for six months duration or longer

and

☐ Patient has tried and not responded to at least three months of oral or parenteral methotrexate at a dose of at least 20 mg weekly or a maximum tolerated dose

and

☐ Patient has tried and not responded to at least three months of sulfasalazine at a dose of at least 2 g per day or leflunomide at a dose of up to 20 mg daily (or maximum tolerated doses)

and

☐ Patient has persistent symptoms of poorly controlled and active disease in at least 15 swollen, tender joints

or

☐ Patient has persistent symptoms of poorly controlled and active disease in at least four joints from the following: wrist, elbow, knee, ankle, and either shoulder or hip

and

☐ Patient has a C-reactive protein level greater than 15 mg/L measured no more than one month prior to the date of this application

or

☐ Patient has an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour

or ESR and CRP not measured as patient is currently receiving prednisone therapy at a dose of greater than 5 mg per day and has done so for more than three months

INITIAL APPLICATION - ankylosing spondylitis – second-line biologic
Applications only from a rheumatologist or Practitioner on the recommendation of a rheumatologist. Approvals valid for 3 months.

Prerequisites (tick boxes where appropriate)

☐ The patient has had an initial Special Authority approval for adalimumab and/or etanercept for ankylosing spondylitis

and

☐ The patient has experienced intolerable side effects from a reasonable trial of adalimumab and/or etanercept

or

☐ Following 12 weeks of adalimumab and/or etanercept treatment, the patient did not meet the renewal criteria for adalimumab and/or etanercept for ankylosing spondylitis

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