Biologic Update in Psoriasis

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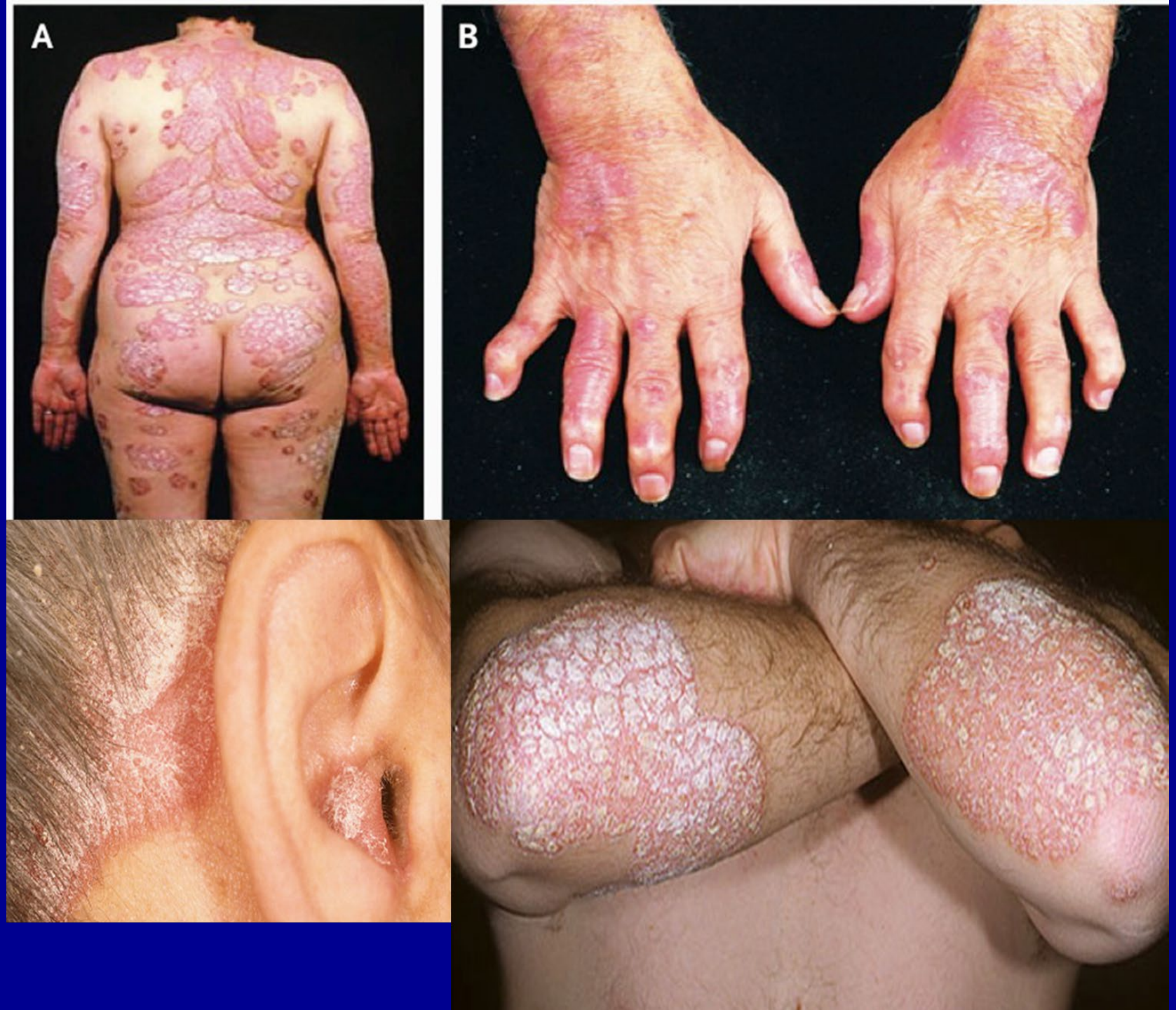

A
B

Biologics: Great therapeutic advance in psoriasis

- Increase in efficacy from methotrexate at about 30% clear or almost clear to almost 90 % at week 16
- From 16 “black box” warnings regarding safety to zero with newer biologics
- Almost no “evidence based” statistically significant side effects with newer biologics

Clinically Focused Review

- 11 agents (excluding Infliximab)
  - Infliximab is almost never used by US dermatologists
  - Bimikizumab is included as an up and coming new biologic agent for psoriasis

TNF Alpha

Blocking Agent

Adalimumab

Adalimumab
TNF-Alpha

- Loading: 80 mg SC at week 0 and 40 mg at week 1
- Maintenance: 40 mg SC q 2 weeks

Adalimumab

TNF-Alpha
Blocking Agent

- **Merits**
- 20+ years of use worldwide in more than 1 million patients for 10 different indications
- FDA approved down to 2 years old for JIA (Juvenile idiopathic arthritis)
- FDA approved for adolescent (12 years and up) for HS
- One of the most efficacious for psoriatic arthritis with FDA recognition for inhibiting joint destruction
- Now available in citrate-free vehicle (with half the volume and smaller needle) which is less painful

- FDA approved medication for inflammatory bowel disease (Chron's and UC)
- ESPIRIT Long Term Registry Data with 10 years of safety data with no new safety signals and events of interest remained low and comparable over time
- PIANO and OTIS registry data showing no increased risk with harmful pregnancy outcomes
- Adalimumab has the best data showing decrease in mortality with treatment compared to a similar population only treated with topicals
- FDA approved specifically for the treatment of nail psoriasis even if the patient does not have generalized BSA greater than 10% psoriasis

- **Demerits**
- More maintenance injection dosing regimen (every 2 weeks)
- Somewhat less efficacious with more injections than with newer agents
- It does have a black box warning
  - Possible Increase risk of TB
  - Possible increased in NMSC
- More tuberculosis concern compared to non-anti-TNF agents

Leonardi C, Papp K, Strober B, Reich K, Asahina A, Gu Y, Beason J, Rozzo S, Tyring S. The long-term safety of adalimumab treatment in moderate to severe psoriasis: a comprehensive analysis of all adalimumab exposure in all clinical trials. Am J Clin Dermatol. 2011 Oct 1;12(5):321-37. doi: 10.2165/11587890-000000000-00000. PMID: 21834597.

Etanercept

Etanercept

TNF-Alpha
Blocking Agent

- Loading: 50 mg SC twice weekly for 12 weeks
- Maintenance: 50 mg weekly

Etanercept
TNF-Alpha

- **Merits**
- 20+ year history of safe use with special safety recognition for the elderly by the FDA
- FDA approved for pediatric use down to 4 years of age
- One of the best biologics for psoriatic arthritis, especially in inhibiting bone and joint destruction
- Much less risk of tuberculosis compared to adalimumab (Humira) or infliximab (Remicade)

- **Demerits**
- Less efficacious with more injections than with newer agents
- More tuberculosis concern compared to non-anti-TNF agents

Certolizumab

Certolizumab

TNF-Alpha
Blocking Agent

Maintenance: 400 mg SC q 2 weeks (No Loading Dose – 2 shots every 2 weeks from the beginning, middle and forever)

Certolizumab
TNF-Alpha

- **Merits**
- Studied in pregnancy; minimal to no transfer into fetal circulation or maternal breast milk
- Approved for Psoriatic Arthritis (one of the best biologics for PsA because outstanding for symptom relief; recognized by FDA as capable of discouraging/stopping joint destruction and bone erosion which is recognized for all anti-TNFs
- ACR recommends anti-TNF as 1st and 2nd line for PsA
- In Phase 3 studies, CZP was able to achieve over 80% (81.6%) PASI 75 achievement rate (CIMPASI 2) by week 16. The data makes CZP notably more effective than any other sub-cutaneous anti-TNFs
- Over 20 year experience in human use
- Over 100,000 patients treated with CZP with 6 indications – PsO, CD, RA, PsA, AS, nrAxSpA (first – only other is ixekizumab (taltz)).
- **Demerits**
- More injections required than with newer agents
- Less long term safety data in PsO than with the other agents (longest safety data available is 3years)

IL 12/23

Ustekinumab

Ustekinumab
IL 12/23

- Patient equal or < 100 kg
- Loading: 45 mg SC at week 0 and 4
- Maintenance: 45 mg SC q 12 weeks

Ustekinumab
IL 12/23

Patient > 100 kg

- Loading: 90 mg SC at week 0 and 4
- Maintenance: 90 mg SC q 12 weeks

Ustekinumab
IL 12/23

- Pediatrics to Adolescent (Age 6 to 17)
- Frequency is unchanged
  - Patient < 60 kg
    - Dose is 0.75 mg/kg
  - Patient is between 60 and 100 kg
    - Dose is 45 mg
  - Patient is between > 100 kg
    - Dose is 90 mg

Ustekinumab
IL 12/23

Merits

- 20+ years of safety data with no evidenced-based increase in side effects
- In USA, ustekinumab has pediatric indication down to age 6 years of age
- No increased tuberculosis risk
- Least injections of all biologic agents available (except Risiankizumab, Tildrakizumab): 1 injection every 3 months
- FDA approved for treatment of inflammatory bowel disease (only IL 12/23 or IL 23 biologic agent with both Chron's and Ulcerative Colitis FDA approval)
- FDA approve for PsA
- Dosing adjustment according to weight is possible (you can give a higher dose to someone with larger body weight which you cannot do with other biologics)
- In IBD, starting dose as high as 520 mg IV given initially (for anybody who is 85 kg or more, followed by maintenance dose of 90 mg every 8 weeks SC) is used routinely with no significant added safety concerns

Demerits

- Somewhat less efficacious than newer agents
- Some patients might experience some worsening of psoriasis in the 3rd month prior to next injection (they may need more frequent injection for example q 8 week dosing which is officially approved in Canada or increasing dose to 90 mg)
- FDA did not bless data regarding inhibition of joint destruction and bone erosion (this is approved in Canadian and European label)

IL 17

Secukinumab

Secukinumab
IL 17

- Loading: 300 mg SC at week 0,1,2,3,4
- Maintenance: 300 mg q 4 weeks
- In some patients 150 mg may be acceptable for maintenance, especially for patients with lower body weight and disease severity

Off label use of increase dosing

- For patients who may need higher dose such as those with more resistant disease and/or heavier body weight, published data is available for possible benefit of secukinumab 300mg every 2 weeks

Secukinumab
IL 17

Merits

- Anti-interleukin 17 with longest track record of safety in real world usage
- One of the best tolerated in terms of injection site reactions/pain
- No black box safety warning
- FDA approval down to 6 yrs old
- No convincing scientific evidence of increased tuberculosis risk
- Most preferred by rheumatologists for the treatment of psoriatic arthritis
- FDA recognized efficacy for inhibiting joint destruction in psoriatic arthritis

Demerits

- Concern regarding increased risk of inflammatory bowel disease (however, the incidence of new-onset IBD is less than 1 out of 1,000 patients on secukinumab)
- Possible slight increase in superficial fungal/yeast infection (fungal rate in phase III study for secukinumab was less than 1%) [mucocutaneous candidiasis 1.2% vs. 0.3% placebo]
- More frequent dosing compared to IL-23 agents

Ixekizumab

Ixekizumab

IL 17 Blocking Agent

- Loading: 160 mg at week 0 then 80 mg at week 2,4,6,8,10,12
- Maintenance: 80 mg q 4 weeks

Ixekizumab

IL 17 Blocking Agent

Merits

- Very high efficacy - possibly the fastest biologic - H2H comparison showed faster onset of action than Guselkumab
- No black box safety warning
- Ixekizumab (Taltz) has been compared H2H against Adalimumab (Humira) for efficacy on PsA, and found to be similar both for symptom control and discouraging joint destruction and bone erosion.
- Only biologic agent with data specifically on genital PsO, which been blessed by FDA
- FDA approval down to 6 years old
- No convincing scientific evidence of increased tuberculosis risk

Ixekizumab

IL 17 Blocking Agent

Demerits

- Higher rate of injection site pain and reaction
  - 97% of patients with reaction refuse to discontinue Phase 3 study and ISR gets better over time.
  - Citrate free new formulation has less than half of the injection site pain of the original formulation
  - New formulation with much less injection site pain and reaction is on the horizon

- Concern regarding increased risk of inflammatory bowel disease (however, the incidence of new-onset IBD is less than 1 out of 1,000 patients on Ixekizumab)
- Possible slight increase in superficial fungal infection (candida rate in phase 3 less than 0.6% for q 4 week dosing)

Brodalumab

Brodalumab

IL 17 Blocking Agent

- Loading: 210 mg SC at weeks 0,1,2
- Maintenance: 210 mg q 2 weeks

Brodalumab
IL 17

Merits

- Very high efficacy (PASI100 achievement in 44% by week 12)
- Unique mechanism of action – blocks the entire IL-17 receptor (only one in class)
- No convincing scientific evidence of increased tuberculosis risk
- Very rapid onset of action reaching statistical significance at week 4 for PASI 100 vs. ustekinumab (stelara) (PASI 75 at week 2 vs. ustekinumab (stelara) and PASI 90 at week 2 vs. ustekinumab (stelara)
- Data for rescue from failure of other biologic agents, this medication frequently succeeds among patients who failed other biologics including other IL-17 agents
- Less than 3% developed anti-bodies and none of them were neutralizing after 52 weeks of treatment
- One year pharmacovigilance data showing no new suicides, new IBD cases or new MACEs. Almost 5 years worldwide pharmacovigilance FDA data showed only 1 suicide in Japan in an elderly terminal cancer patient who may have had only 1 dose
- Least expensive biologic. Even analysis by a competitor company showed that brodalumb was most cost effective.

Demerits

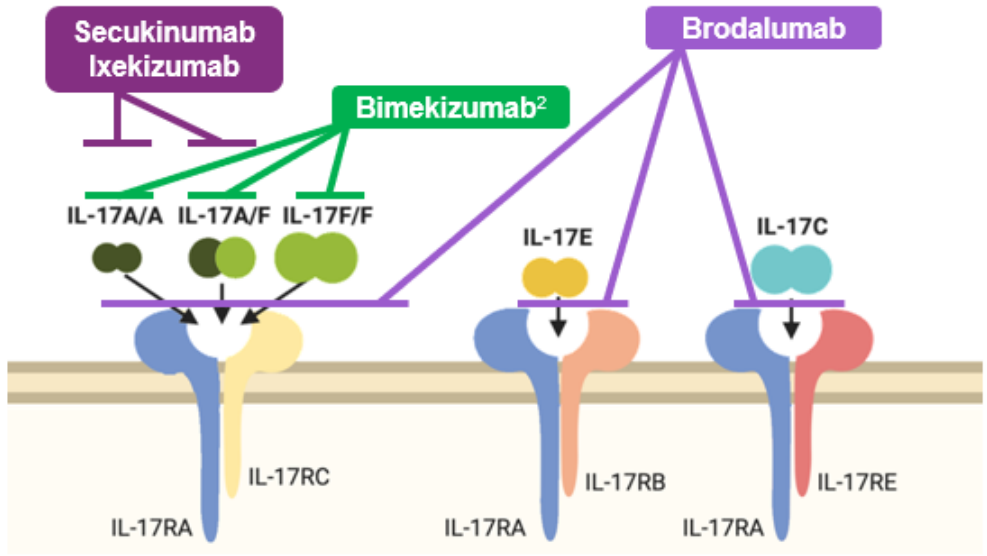
- Black box warning on suicide based on 3 suicides out of 4,464 research subjects, occurring in 2 research sites out of 390 research sites worldwide; no suicide warning anywhere in the world except in the USA courtesy of the FDA. Patients were not excluded from phase 3 study for history of suicidal ideation/behavior unlike other studies (REM requirement)
- Concern regarding increased risk of inflammatory bowel disease (however, the incidence of new-onset IBD is 1 out of 4,464 patients on brodalumab)
- Slight increase in superficial fungal/yeast infection vs. placebo - candida less than 1% but slightly higher than placebo .9 vs .2%; just like all other IL-17s

Bimekizumab

pending FDA approval

Bimekizumab targets IL-17A and IL-17F, key drivers of the pathogenesis of psoriasis

IL-17 cytokines, receptors, and inhibitors[1,2]



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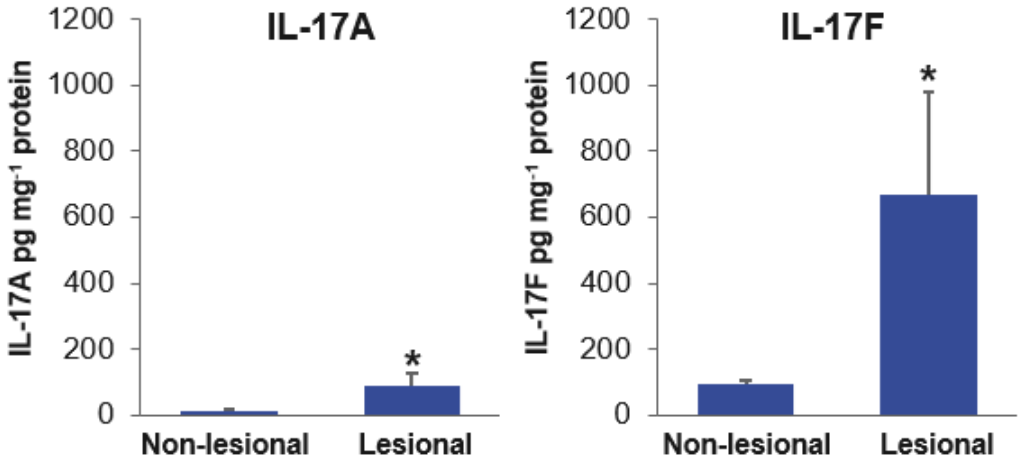
IL-17 protein expression in patients with psoriasis[3]



- The cytokines IL-17A and IL-17F have overlapping biology and are key drivers of the pathogenesis of psoriasis[2,4,5]
- IL-17F drives inflammation independently from IL-17A[2]
- IL-17A and IL-17F are both upregulated in psoriatic skin lesions[3]
- Pre-clinical data show that bimekizumab is a targeted inhibitor of both IL-17F and IL-17A[2]

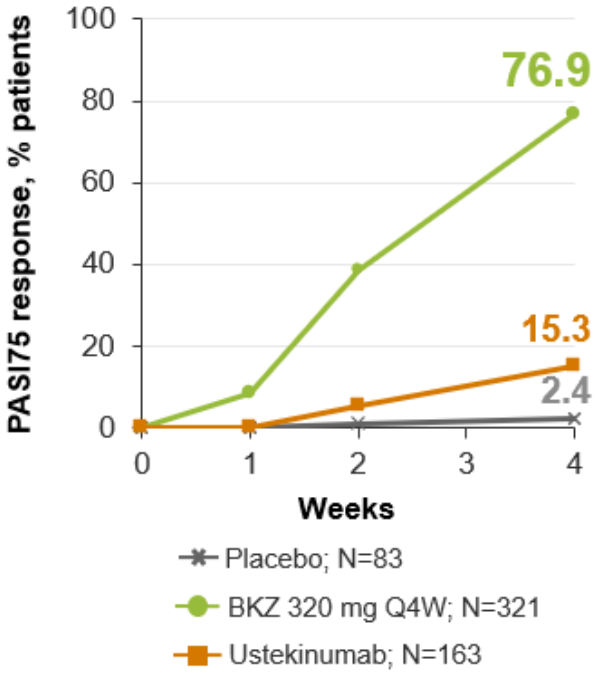
* $p<0.05$ versus non-lesional psoriatic skin

Bimekizumab: PASI75 through week 4 (NRI)

PASI75 at week 4* shows superior efficacy after one dose of BKZ

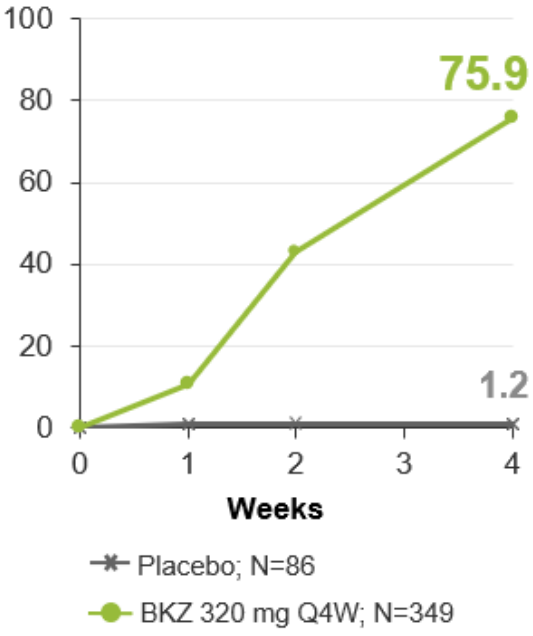
BKZ superiority: all comparisons (in all trials) $P<0.001$

Vs Ustekinumab



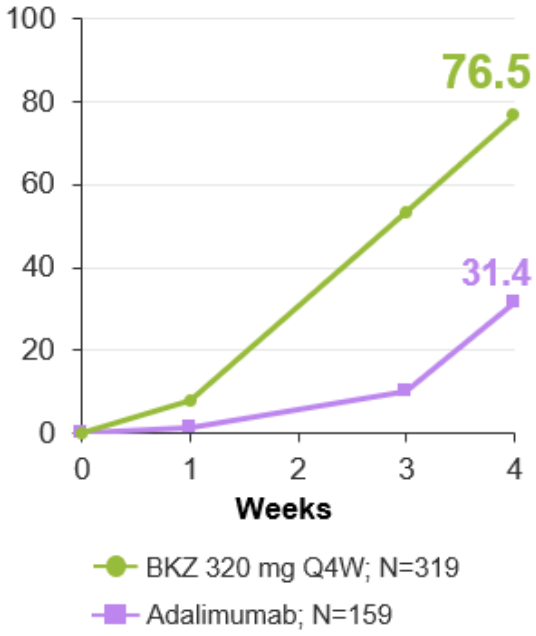
Adapted from Reich et al. Lancet 2021

Vs Placebo



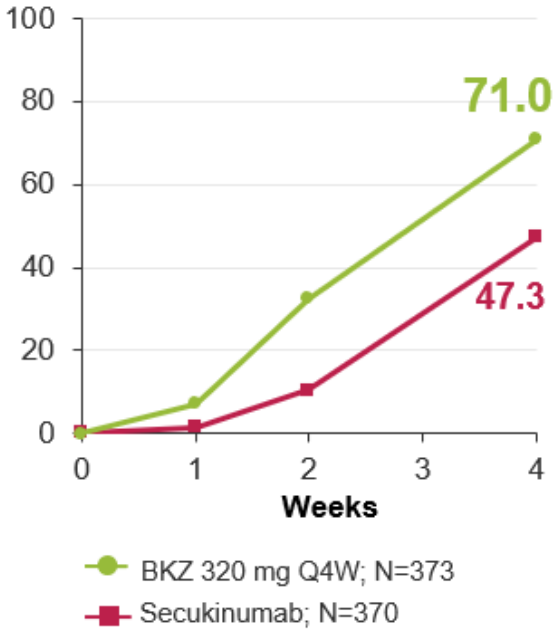
Adapted from Gordon et al. Lancet 2021

Vs Adalimumab



Adapted from Warren et al. N Engl J Med 2021

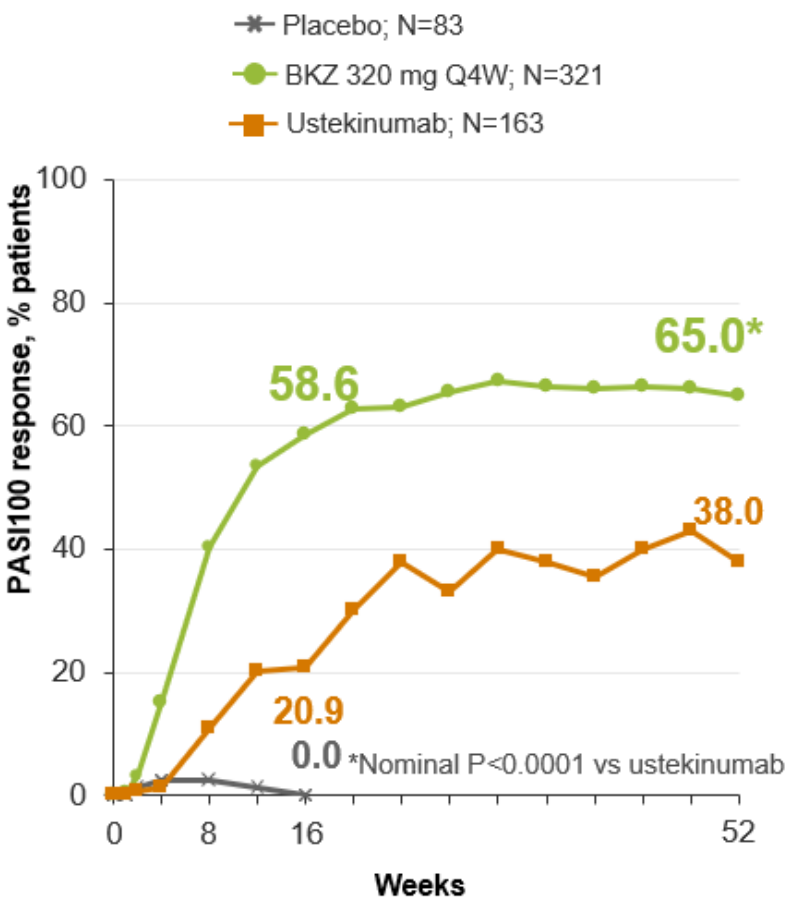
Vs Secukinumab



Adapted from Reich et al. N Engl J Med 2021

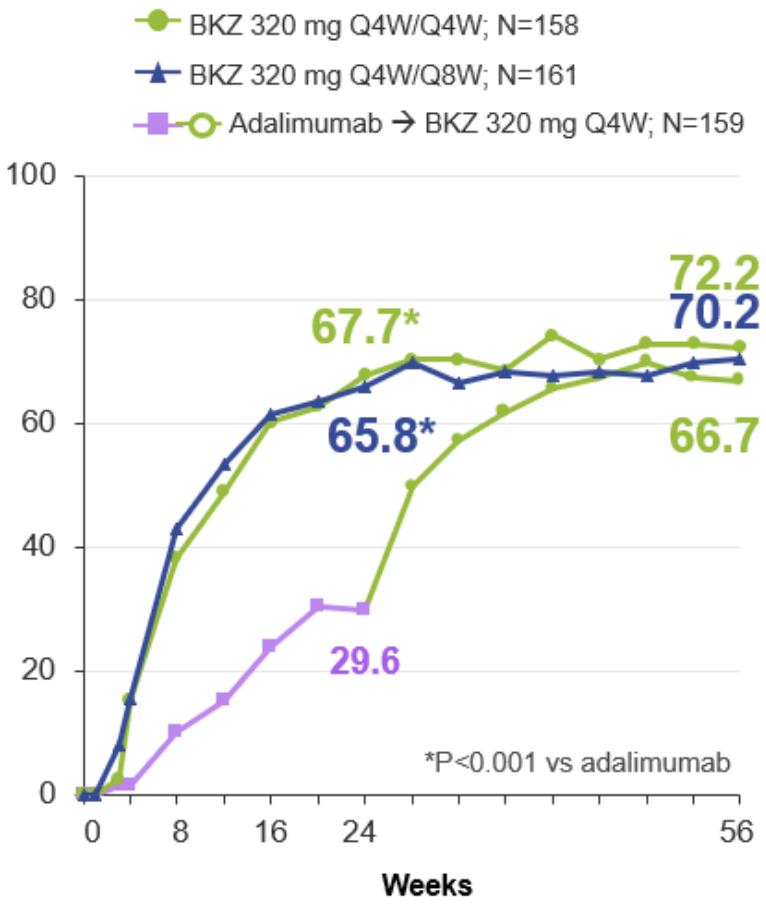
Bimekizumab: PASI100 over ~1 year vs active comparators (NRI)

Vs Ustekinumab



Adapted from Reich et al. Lancet 2021

Vs Adalimumab



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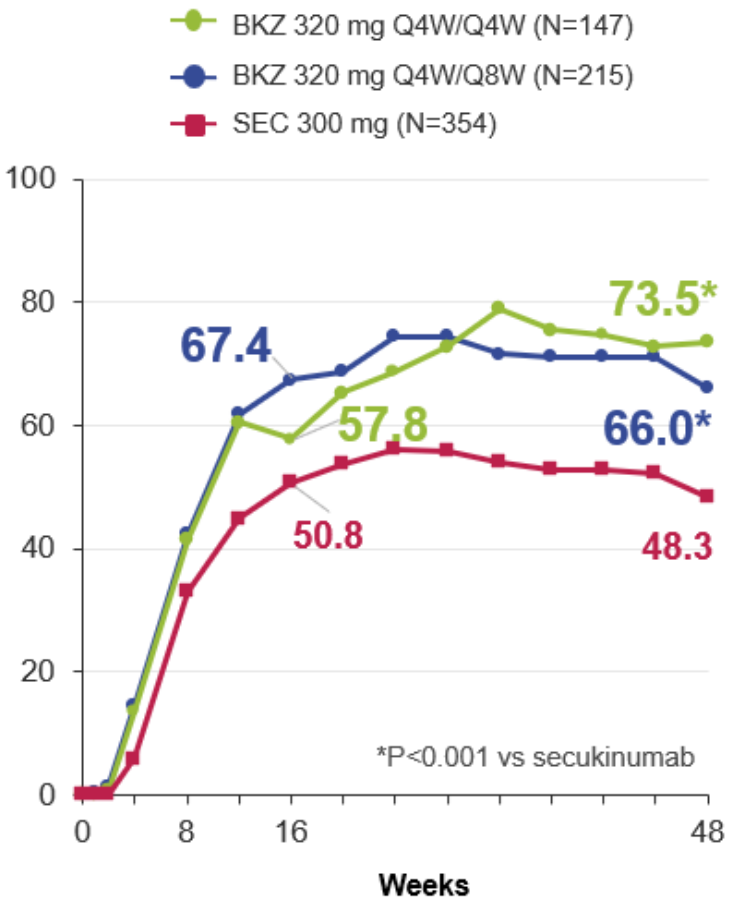
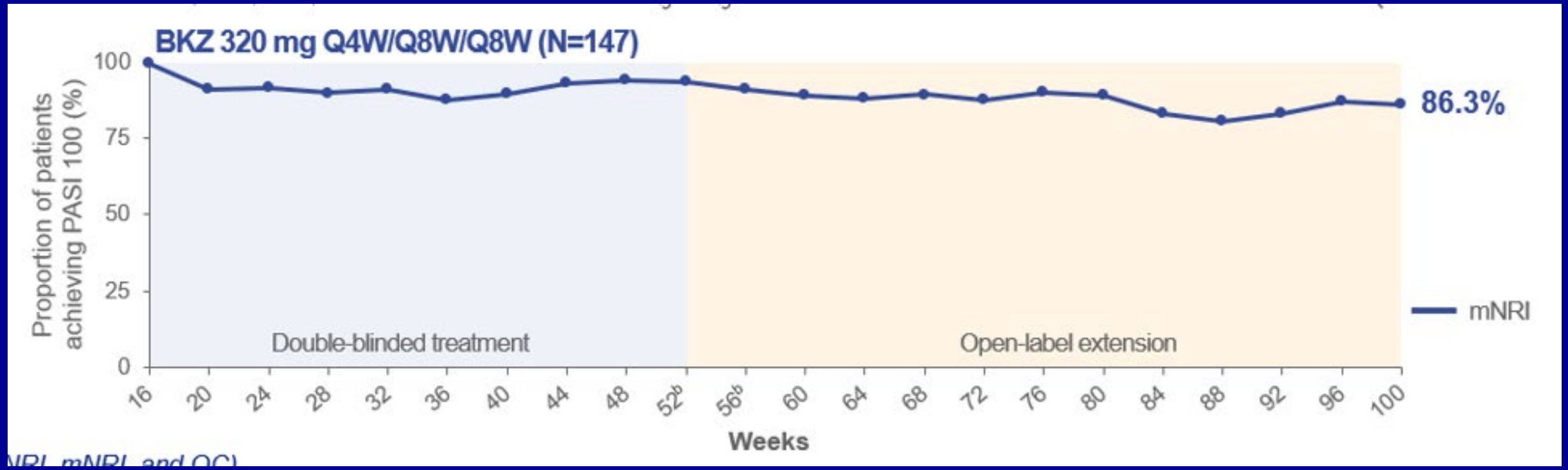
Vs Secukinumab



Adapted from Reich et al. N Engl J Med 2021

Bimekizumab 2 year maintenance of PASI 100 (Maintenance every 8 weeks)



Bimekizumab Safety
Head to Head against Adalimuamb/Ustekinumab

	Initial treatment period (Week 0–16)			
	n (%)			
	BKZ 320 mg Q4W[a] N=989	ADA[b] N=159	UST[c] N=163	PBO[d] N=169
Exposure	306.0 PY	48.8 PY	50.1 PY	51.6 PY
Any TEAE	593 (60.0)	96 (60.4)	83 (50.9)	74 (43.8)
Serious TEAEs	15 (1.5)	3 (1.9)	5 (3.1)	4 (2.4)
Discontinuation due to TEAEs	17 (1.7)	4 (2.5)	3 (1.8)	7 (4.1)
Drug-related TEAEs	212 (21.4)	32 (20.1)	19 (11.7)	15 (8.9)
Severe TEAEs	12 (1.2)	4 (2.5)	3 (1.8)	4 (2.4)
Deaths	1 (0.1)	1 (0.6)	1 (0.6)	1 (0.6)

TEAEs of interest short- and longer-term

Short- and longer-term TEAEs[1]	Initial treatment period (Week 0–16)				Short-term (Week 0–16)	1 year
	n (%)				EAIR per 100 PY (95% CI)	
	BKZ 320 mg Q4W[a] N=989	ADA[b] N=159	UST[c] N=163	PBO[d] N=169	BKZ 320 mg Q4W[a] N=989	All BKZ[e] N=1,789
Exposure	306.0 PY	48.8 PY	50.1 PY	51.6 PY	306.0 PY	1830.4 PY
Serious infections	3 (0.3)	0	2 (1.2)	0	1.0 (0.2, 2.9)	1.4 (0.9, 2.0)
Inflammatory bowel disease	1 (0.1)	0	0	0	0.3 (0.0, 1.8)	0.1 (0.0, 0.3)
***Candida* infections**	90 (9.1)	0	0	0	30.6 (24.6, 37.6)	18.7 (16.7, 21.0)
Oral candidiasis	75 (7.6)	0	0	0	25.3 (19.9, 31.8)	16.4 (14.5, 18.5)
Adjudicated MACE	1 (0.1)	0	0	0	0.3 (0.0, 1.8)	0.7 (0.3, 1.1)
Malignancies (inc. NMSC)	4 (0.4)	1 (0.6)	0	1 (0.6)	1.3 (0.4, 3.4)	0.8 (0.5, 1.4)
Adjudicated SIB*	0	0	0	0	0	0.1 (0.0, 0.3)
Serious hypersensitivity reactions†	0	0	0	0	0	0.2 (0.0, 0.5)
Injection site reactions	27 (2.7)	3 (1.9)	2 (1.2)	2 (1.2)	9.0 (5.9, 13.1)	3.1 (2.4, 4.1)
Hepatic events	19 (1.9)	9 (5.7)	0	2 (1.2)	6.3 (3.8, 9.8)	5.6 (4.6, 6.8)

- BE RADIANT data not included. In BE RADIANT incidence of TEAEs of safety topics of interest was generally similar in the bimekizumab group compared with the secukinumab group, except for candidiasis, where incidence was higher in bimekizumab-treated participants[2]

*One event adjudicated as active suicidal ideation with some intent to act in a patient with pre-existing psychiatric conditions
†Includes one fatal event of circulatory failure (adjudicated MACE), one event of atopic dermatitis-like disseminated eczema and one case of anaphylactic shock due to insect sting

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Incidence of oral candidiasis between doses over 2 years in the phase 3 feeder studies

Oral candidiasis rate over 2 years[1] (BKZ Total: median exposure 730 days[2])	All patients who received BKZ in the phase 3 feeder studies (BE VIVID, BE READY, BE SURE) or the OLE (BE BRIGHT)[a]		
	BKZ 320 mg Q4W (N=1,456) EAIR/100 PY (95% CI)	BKZ 320 mg Q8W (N=930) EAIR/100 PY (95% CI)	BKZ Total (N=1,495) EAIR/100 PY (95% CI)
Oral Candidiasis	16.4 (14.5, 18.5)	9.6 (7.6, 12.0)	12.9 (11.5, 14.4)

Key points

- The IR of oral candidiasis decreased with prolonged bimekizumab exposure[3]
  - The IR over 2 years was 12.9 / 100 PY (95% CI: 11.5, 14.4)
- The incidence rate of oral candidiasis tended to be lower on BKZ Q4W/Q8W than BKZ Q4W/Q4W[4]

BE RADIANT data not included. Similar results for candidiasis seen in BE RADIANT vs the pooled analysis[5]

[a] Includes all patients who received BKZ during any of the phase 3 feeder studies (BE VIVID, BE READY, BE SURE) or the OLE (BE BRIGHT); the data cut-off for the ongoing BE BRIGHT trial was Nov 2020. TEAEs were assigned to the dose most recently received prior to the date of onset of the TEAE. Patients who received both BKZ 320 mg Q4W and Q8W at different times in the trials are included in the population count of both treatment groups, but only once in each BKZ total group.

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Bimekizumab

IL 17A and IL17F Blocking Agent

Merits

- Likely the most efficacious agent for psoriasis and, when when we the dermatologists use it, possibly also the most efficacious agent for psoriatic arthritis

Demerits

- Higher rates of oral candidiasis

IL 23

Guselkumab

Guselkumab
IL 23

- Loading: 100 mg SC at week 0 and 4
- Maintenance: 100 mg q 8 weeks

Guselkumab
IL 23

"One-press" injector

Merits

- Very high efficacy
- No black box warning
- No convincing scientific evidence of increased tuberculosis risk
- No concern ever raised about risk of inflammatory bowel disease.
- No FDA warning of increased risk of superficial tinea or candida infections in the package insert in the warning and precautions section
- Psoriatic Arthritis indication
- After 48 weeks of therapy, PASI 90 efficacy is superior to secukinumab from H2H comparison study (ECLIPSE study)
- Convenience maintenance dosing, every 2 months dosing
- Convenient delivery system with less pain then auto injector (One-Press Injector)
- Sub analysis from H2H comparison with adalimumab showed that guselkumab Was superior in efficacy vs. adalimumab for scalp and palmoplantar psoriasis but similar for nail psoriasis
- Tested and approved by Japanese regulatory agency for palmoplantar pustulosis

Demerits

- Onset of action is slower than ixekizumab from H2H comparison study - however by week 24 the results were similar (Guselkumab PASI 100 rate was numerically higher)

Tildrakizumab

Tildrakizumab
IL 23

- Loading: 100 mg at week 0 and 4
- Maintenance: 100 mg q 12 weeks

Tildrakizumab
IL 23

Merits

- Only biologic for psoriasis guaranteed to be covered by Medicare part B (medical benefit, not just prescription benefit with “donut hole”) because this is the only biologic where injection is required to be given by the provider (not self-injection)
- Only 4 injections per year for maintenance dose
- High re-capture rate: 85.7-96.1% of patients will be regain response (PASI 75) after retreatment
- Long “time to relapse” duration (for PASI 75 responders, it took median of 7.5 months [226 days] to lose half of their best response)
- Very safe biologic profile: According to package insert, this has the least number of adverse events occurring at least 1% in phase III of all the biologics for psoriasis available (only 3 items –URI, injection site reaction and diarrhea); No black box warning
- **Demerits**
- Not yet approved for psoriatic arthritis
- Onset of action is slower than other IL 23 agents (efficacy peaks slower)

Risankizumab

Risankizumab

IL 23 Blocking Agent

- Loading: 150 mg SC at week 0 and 4
- Maintenance: 150 mg q 12 weeks

Risankizumab

IL 23 Blocking Agent

Merits

- Very high efficacy (Onset of action as fast as secukinumab and better efficacy by week 52)
- Only 4 injections per year for maintenance dose (one dose per 3 months)
- No black box warning (not clear what is the evidence based side effect – even injection site reaction is similar to placebo)
- High Durability (after discontinuation, responders took mean of 295 days to recur psoriasis at the level of moderate or worse)
- 31 psoriasis patients with latent TB who were treated with risankizumab but never received anti-TB medication did not reactivate TB (IMMHANCE – phase III study)

Demerits

- Not recognized by FDA that risankizumab can discourage joint destruction and bone erosion in psoriatic arthritis (guselkumab does not have this recognition either)

Thank You!