EMJ DERMATOLOGY

European Edition — Suppl. 2 February 2020 emjreviews.com

+ EADV 2019 & WCD 2019

New Insights into Psoriasis Treatment

Contents

Biologics in Moderate-to-Severe Psoriasis: Discover the Road to Long-term Control

This symposium took place on 10th October 2019, as part of the 28th European Academy of Dermatology and Venereology (EADV) Congress in Madrid, Spain

Chairperson: Diamant Thaçi[1]

Speakers: Stefano Piaserico,[2] Diamant Thaçi,[1] Luis Puig[3]

1. Comprehensive Centre of Inflammation Medicine, University of Lübeck, Lübeck, German
2. Dermatology Unit, Department of Medicine, University of Padua, Padua, Ital
3. Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

Disclosure: Prof Thaçi has provided research support or been a consultant, lecturer, or advisor board member for AbbVie, Amgen, Almirall, Biogen-Idec, BioSkin, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Chugai, Dermira, Dignity, Eli-Lilly, Forward-Pharma, Galapagos, GlaxoSmithKline, Janssen-Cilag, La Roche-Posay, Leo-Pharma, Maruho, Mitsubishi Pharma, Morphosis, Merck Sharp & Dohme, Mundipharma, Novartis, Pfizer, Regeneron, Roche, Sandoz-Hexal, Sanofi, UCB, and Xenoport. Prof Piaserico has been a speaker for or received honoraria, grants, or research supports from AbbVie, Almirall, Amgen, Celgene, Galderma, Janssen, Leo-Pharma, Lilly, Merck-Serono, Merck Sharp & Dohme, Novartis, Pfizer, Sandoz, Sanofi, and UCB. Prof Puig has been a speaker for or received honoraria, grants, or research supports from AbbVie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Gebro, Janssen, Leo-Pharma, Lilly, Merck-Serono, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Roche, Sandoz, Sanofi, and UCB.

Acknowledgements: This symposium was EACCME accredited and managed by EPG Health. Medical writing assistance was provided by Nadine Engelbert.

Support: Almirall sponsored this event via an education grant. The views and opinions expressed are those of the presenters. Content was reviewed by Almirall for medical accuracy.

Citation: EMJ Dermatol. 2020;8[Suppl 2]:3-11.

Meeting Summary

This symposium took place on 10th October 2019, as part of the 28th European Academy of Dermatology and Venereology (EADV) Congress in Madrid, Spain. The symposium provided an overview of the advances in treatment of moderate-to-severe psoriasis over recent years, with a focus on IL-23 and IL-17 inhibitors. Prof Piaserico explained the mechanism of action of the new biologic therapies and their potential positive impact on both psoriasis and other comorbid conditions. Long-term disease control was identified as a continued unmet need which is of utmost importance to both the clinician and patient. Prof Piaserico described how psoriasis should be viewed as a marathon rather than a sprint. Prof Thaçi reiterated the need to review the efficacy and safety of biologic treatments following experience in everyday clinical practice, which can differ significantly from the data obtained from

clinical studies. He emphasised the importance of obtaining a patient profile before initiating treatment and increasing adherence to treatment through regular patient reviews. The effects of the cessation of treatment on long-term disease was discussed. Prof Puig elicited from the symposium audience that their main concern regarding biologic use in moderate-to-severe psoriasis was the potential associated risk of infection. His presentation focussed on the safety data available for these therapies, both from national clinical registries and clinical studies, concluding that IL-23 inhibitors are associated with a significantly lower rate of overall adverse events than that of IL-17 inhibitors. The symposium concluded with a dynamic question and answer session.

Mind the Gap - The Benefits of Modern Biologic Treatment

Professor Stefano Piaserico

Advances in the treatment of moderate-to-severe psoriasis have accelerated considerably in the last 30 years. Prof Piaserico provided an overview of the pathogenesis of psoriasis. This begins with activation of dendritic cells by TNFα and IFNα, which is influenced by genotype, environmental factors, stress, and trauma. Activation of dendritic cells produces IL-23 which leads to differentiation of TH17 cells, Type 3 innate lymphoid cells (ILC3), and γδT cells. These cells produce IL-17, IL-22, and other proinflammatory markers which induce neutrophil and keratinocyte activation and proliferation. Keratinocytes produce other cytokines which recruit additional inflammatory cells (TH17, neutrophils, and macrophages), inducing a vicious circle which maintains the chronicity of psoriatic plaque formation.[1-3]

When psoriasis was discovered to be an immunologic disease, treatments involved broad spectrum immunosuppressive therapy, explained Prof Piaserico. TNFα inhibitors then became the mainstay of treatment. More recently, treatment has become highly specific, targeting IL-17, IL-12/23p40, and IL-23p19.[1,4] Furthermore, studies have suggested the additional potential positive impact of IL-23 and IL-17 inhibitors on patients with depression, adipose tissue inflammation in obesity, and nonalcoholic fatty liver disease.[5-9]

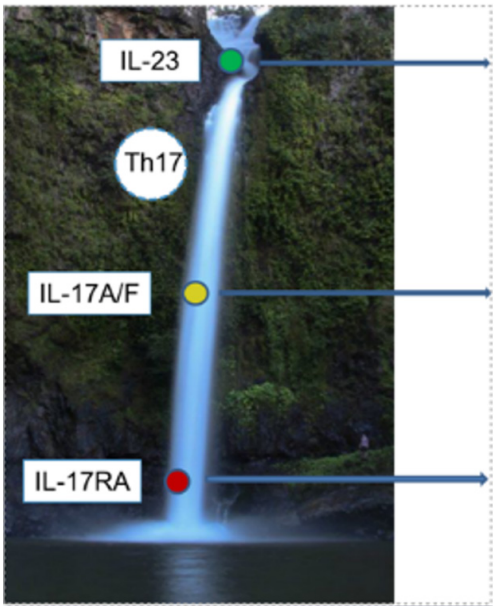
Targeting IL-23 and IL-17: Impact on Patients

In the presence of IL-12, dendritic cells activate proliferation of Th1 cells, whilst activity of dendritic cells in the presence of IL-4 produces Th2 cells. The presence of IL-6 and TGF-β generates Th17-inducible cells, which can be modified in the absence of IL-23 into nonpathogenic Th17 cells which produce IL-17 and IL-10. In the presence of IL-23, Th17 inducible cells can be modified into pathogenic Th17 cells which produce IL-17 and IL-22.[9-11]

Prof Piaserico explained the mechanism of the IL-23/Th17 axis using the analogy of a cascade (Figure 1).[12] Blocking the IL-17 receptor (e.g., with brodalumab), a downstream target, has a fast onset of action, but more frequent dosing is required, and quick relapse may occur when the drug is stopped. Blockade of IL-17 itself (e.g., with ixekizumab or secukinumab), a midstream target, results in a slightly slower onset of action than IL-17 receptor blockade; however, less frequent dosing is required. Blocking IL-23 (e.g., with tildrakizumab, guselkumab, or risankizumab), an upstream target, blocks the entire cascade with less frequent dosing required, which may be more convenient for the patient. The onset of action may be slower, but there may be the potential to modify the underlying disease process. In addition, IL-23 blockade may have a positive impact on inflammatory bowel disease because nonpathogenic Th17 cells are still present, allowing production of IL-17 which preserves the intestinal epithelial barrier despite its potential to drive pathogenic inflammation.[13] The risk of candidiasis may also be lower with IL-23 inhibitors.[14] There is a theoretical benefit of IL-23 inhibitors in spondyloarthritic disease, due to the effect on IL-22 which enhances new bone deposition in psoriatic arthritis.[15]

Unmet Needs

Despite advances, Prof Piaserico highlighted that there are still unmet needs: in particular, long-term disease control. One study has shown that patients rate maintenance of response to treatment over time as one of the most important drug characteristics, rating it higher than rapidity of response after initiating treatment.[16]



Upstream target
- Infrequent dosing
- No rebound
- Slightly slower onset of action
- Potential to modify underlying disease

- Tildrakizumab
- Guselkumab
- Risankizumab

Midstream target
- Frequent dosing
- Less rebound
- Quick onset of action

- Ixekizumab
- Secukinumab

Downstream target
- More frequent dosing
- More rebound
- Quicker onset of action

- Brodalumab

Figure 1: Cascade – the IL-23/TH17 axis in the pathogenesis of psoriasis.
Reproduced with permission from Prof Piaserico, EADV 2019.[12]

Pooled data from two randomised controlled Phase III trials studying the efficacy and safety of tildrakizumab (reSURFACE 1 and reSURFACE 2) showed that efficacy was maintained in Week 28 responders (≥75% improvement in Psoriasis Area and Severity Index [PASI 75]) through to 3 years.[17,18]

After long-term control, a decision must be made regarding a long-term treatment plan. In reSURFACE 1, PASI 75 responders who received their last dose of tildrakizumab at Week 16 showed a median time to relapse of 32 weeks (tildrakizumab 100 mg) or 36 weeks (tildrakizumab 200 mg).[17,18] Prof Piaserico highlighted that this demonstrates control in >90% of patients 7 months after the last dose. A long-term adalimumab open-label extension study showed that when adalimumab was withdrawn in the subgroup of patients with stable psoriasis control (n=285), relapse occurred in approximately 60% of patients (n=178), with a median relapse time of 141 days.[19]

Data are lacking regarding the tapering down of treatment. Mostly uncontrolled emerging data indicate that a dose reduction of TNFα inhibitors can be achieved in a relevant proportion of patients with rheumatoid arthritis without losing clinical efficacy.[20,21] Tapering down treatment reduces cost and dose-dependent side-effects.[22-25]

En Route to Long-Term Control?

Professor Diamant Thaçi

Prof Thaçi began his presentation by asking the audience what the most important factor is, for them as a physician, in the treatment of moderate-to-severe psoriasis. They voted in the majority for remission.

Prof Thaçi acknowledged that review of available evidence often does not help distinguish which treatment has the greatest long-term efficacy.[26] Head-to-head trials help guide clinical practice; however, results may differ in everyday practice as the population responds differently to subjects in the clinical trial, which have often been selected according to previous treatments.

Differing rates of drug survival are seen in clinical registries. Drug survival reflects a drug's effectiveness, safety, and tolerability. The British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR) assessed the drug survival of biologics used to

treat psoriasis in a prospective national pharmacovigilance cohort. Multivariate analysis showed that factors including female sex, being a current smoker, and a higher baseline dermatology life quality index were predictors of discontinuation. Presence of psoriatic arthritis was a predictor for drug survival.[27] Drug survival has also been assessed from the Danish registry DERMBIO (Danish Biologics Interventions Registry), which collects data on all Danish patients with moderate-to-severe plaque psoriasis treated with biologics.[28] Analysis of data collected between 1st January 2007 and 31st March 2017 showed that ustekinumab was associated with the highest drug survival and secukinumab with the lowest, although most patients on secukinumab were non-naïve. Switching from originator to biosimilar had no significant impact on drug survival, and the safety profiles were comparable. Adverse events occurred most frequently with secukinumab.[28]

Prof Thaçi acknowledged that his patients most appreciate continuous improvement without loss of response. Continuous improvement can be encouraged by seeing patients regularly to encourage treatment adherence.

Gone but Not Forgotten

Tildrakizumab was the first IL-23 inhibitor that Prof Thaçi had experience with. In two Phase III trials, reSURFACE 1 and reSURFACE 2, tildrakizumab 200 mg and 100 mg were efficacious compared with placebo and etanercept, and were well-tolerated in the treatment of patients with moderate-to-severe chronic plaque psoriasis.[17]

With TNFα inhibitors, we have learnt that disease improves but is still present: 'gone but not forgotten'. reSURFACE 1 and reSURFACE 2 demonstrated a maintained improvement in PASI scores through to Week 148, without the fluctuations that are often experienced with other treatments.[17] This effect seems to be common with all IL-23 inhibitors.

Stopping treatment with IL-23 inhibitors after long-term control seems to produce an effect which cannot be explained pharmacokinetically. The disease recurs but in a very slow manner. The median time to relapse after stopping treatment with tildrakizumab 100 mg is 224 days, or 252 days with tildrakizumab 200 mg (p=0.09).[18]

Similar results have been seen with guselkumab in two Phase III studies, VOYAGE 1 (N=837) and VOYAGE 2 (N=992). These randomised controlled trials demonstrated that guselkumab was superior to adalimumab in improving health-related quality of life, which was associated with greater skin clearance.[29]

Understanding psoriasis pathogenesis is still a puzzle but the pieces are slowly coming together, explained Prof Thaçi. The phenotype of the disease is changing but we are learning more about how to manage this systemic disorder. Psoriasis comorbidities are relevant for dermatologists when managing patients. It is important to consider the inflammatory processes affecting the skin and systemic symptoms, as well as the cardiovascular and psychiatric comorbidities. Quality of life and burden of disease must be reviewed when assessing treatment efficacy and patient satisfaction.[30]

Targeting Safety in Treatment Decisions

Professor Luis Puig

Prof Puig began by eliciting from the audience that their main concern regarding biologic use for moderate-to-severe psoriasis is the associated risk of infection. He reassured the audience that there is good safety data available to support the use of biologics.

There are many cytokines involved in the immune defence system against infections (Figure 2).[14] IL-12 blockade may be harmful, with particular concern regarding infections such as tuberculosis and salmonella because IL-12 acts on both innate and adaptive lymphoid cells to produce IFNγ, which has a key role in preventing tumour initiation, growth, and metastases.[14,31] IL-17 receptor blockade may lead to an increase in infections such as *Staphylococcus aureus* and *Candida albicans*.[14] IL-23 blockade may be beneficial as it is known that IL-23 is overexpressed in human carcinoma and it can promote tumour growth indirectly.[14]

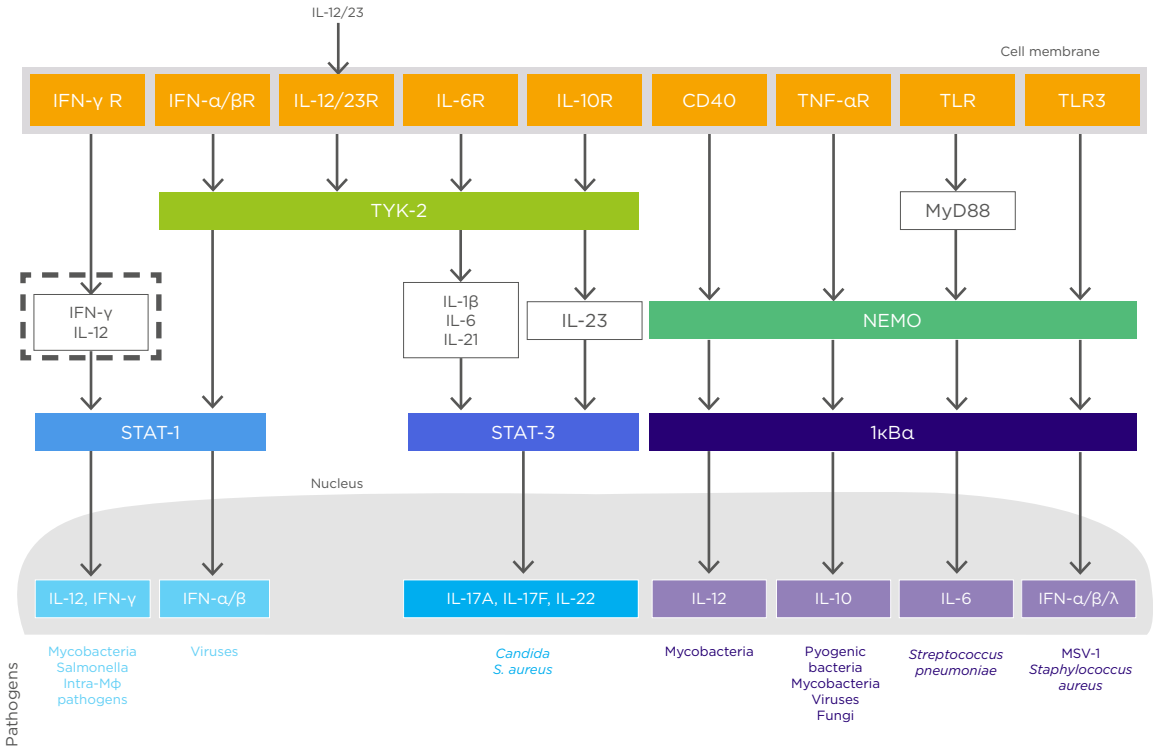


Figure 2: The role of cytokines in the pathogenesis of psoriasis and immune defence against infectious agents.
CD: cluster of differentiation; HSV: herpes simplex virus; Mϕ: macrophage; NEMO: nuclear factor-kB essential modulator; STAT: signal transducer and activator of transcription; TYK: tyrosine kinase.
Adapted from Blauvelt et al.[14]

There are several comorbidities associated with psoriasis, for example, dermatological malignancies, myocardial infarction, and diabetes.[32] Diabetes has the highest attributed risk in severe psoriasis, at 3.67 per 1,000 person-years. The attributed risk for melanoma is 0.05 per 1,000 person-years, with a number needed to harm of 20,135 patients due to the low prevalence of melanoma overall in the population.[32] The main risk factor for myocardial infarction is age, so the number needed to harm is much higher in younger patients.[32]

Safety Data from Clinical Registries

Prof Puig summarised available registry data comparing safety of biologics for psoriasis. PSOLAR (Psoriasis Longitudinal Assessment and Registry), PsoBest (German Psoriasis Registry), and BIOBADADERM (Spanish Registry of Adverse Events Associated With Biologic Drugs in Dermatology) have collected data comparing safety of treatment with TNFα inhibitors and IL-12/23 inhibitors.[33-35] Between 2008 and 2013, 1,030 patients received biologics and 926 patients received classic systemic treatment. The age- and gender-adjusted hazard ratio (HR) of adverse events was lower in the biologics group (HR: 0.60; 95% confidence interval [CI]: 0.5–0.7), with no difference in rates of serious and mortal adverse events. There was an increased raw relative risk (1.5; 95% CI: 1.2–1.8) of infections and infestations in patients who had received biologics.[33] The overall risk of adverse events was not higher in the elderly (≥65 years, 9.8% of patients on the registry, drug group-adjusted HR: 1.09; 95% CI: 0.93–1.3), however serious adverse events were more common in the elderly (drug group-adjusted HR: 3.2; 95% CI: 2.0–5.1). Age-adjusted HR of all adverse events was lower for patients exposed to biologics compared to classic drugs (HR: 0.7; 95% CI: 0.6–0.7). Age did not seem to modify the effect of therapy (biologic versus classic) in the risk of adverse events.[34] The BIOBADADERM registry has shown that combination treatment with methotrexate generally increases infection risk.[35]

PsoBest showed that in a total of 2,444 patients (1,791 patients on conventional systemic drugs, 908 patients on biologics), there was no significant difference in the risk of severe cardiovascular events between single conventional and biologic treatments.[36]

Data were analysed from 11,466 patients in PSOLAR at dermatology centres. A higher risk of serious infections was seen with adalimumab and infliximab compared with nonmethotrexate and nonbiologic therapies; however, no increased risk was seen with ustekinumab or etanercept.[37] PSOLAR has also analysed data regarding risk of malignancy. Methotrexate and ustekinumab were not associated with an increased risk of malignancy, however treatment with TNFα inhibitors was associated with a significantly increased risk of malignancy over a 24-month exposure period.[38]

Clinical Study Safety Data

Clinical studies also provide important safety data regarding biologic treatment, as reviewed by Prof Puig. A systematic review and meta-analysis has shown that there is no significant difference between biologics and placebo in the risk of serious infection in patients with psoriasis at Weeks 12–16 (overall pooled Peto odds ratio: 0.71; 95% CI: 0.36–1.41) and Weeks 20–30 (odds ratio: 2.27; 95% CI: 0.45–11.49).[39] Prospective cohort study data of low quality suggests that only adalimumab (adjusted HR: 2.52; 95% CI: 1.47–4.32) was associated with a significantly higher risk of serious infection compared with retinoid and/or phototherapy in adults.[39]

In a cohort of adult Kaiser Permanente Northern California health plan members with psoriasis diagnosed from 1998 to 2011 and treated with at least one systemic antipsoriatic agent, malignancy rates were calculated, adjusting for presence of psoriatic arthritis, prior ultraviolet light therapy, BMI, and cigarette use.[40] Overall incident cancer rates were comparable between ever-biologic as compared to nonbiologic users. Nonmelanoma skin cancer rates were 42% higher among individuals ever exposed to a biologic, largely driven by increased cutaneous squamous cell carcinoma risk.

An observational cohort study was conducted using medical and outpatient pharmacy claims from two large USA health insurance claims databases from 2003 to 2015. The pooled propensity score-matched analysis yielded a decreased rate of overall serious infection in users of apremilast, etanercept, and ustekinumab, compared with methotrexate.[41]

A pooled safety analysis of IL-17 and IL-23 inhibitors has shown that IL-17 inhibitors are highly efficacious but are associated with a significantly higher rate of overall adverse events than that of IL-23 inhibitors.[42,43] It may therefore be harder to achieve a good balance between safety and efficacy with IL-17 inhibitors. ECLIPSE, a Phase III randomised controlled trial, showed superior long-term efficacy with guselkumab, based on PASI 90 at Week 48, when compared with secukinumab for treating moderate-to-severe psoriasis.[44] However, proportions of patients with adverse events, infections, and serious adverse events were similar between the two treatments.

Two Phase III randomised controlled trials, reSURFACE 1 and reSURFACE 2, assessed the long-term efficacy and safety of tildrakizumab in moderate-to-severe psoriasis for up to 148 weeks.[17] Tildrakizumab was well-tolerated. Safety in the tildrakizumab 100 mg and 200 mg groups was compared with the etanercept 50 mg group. The main difference in the 148–week cumulative exposure–adjusted incidence rates of adverse events was in the rate of injection site reaction in terms of events per 100 patient years of exposure (1.94 with tildrakizumab 100 mg; 2.30 with tildrakizumab 200 mg; 40.41 with etanercept).[17] Another two randomised controlled trials, UltIMMa-1 and UltIMMa-2, showed similar treatment-emergent adverse event profiles between ustekinumab and risankizumab, with no unexpected safety findings.[45]

Prof Puig ended by reiterating that class-specific adverse events occur less frequently with IL-17 and IL-12/23 inhibitors than with TNFα inhibitors, however paradoxical reactions have occurred with IL-17 and IL-12/23 inhibitors. Available data from IL-23p19 inhibitors have not shown an increased risk of specific infections or malignancies, however long-term data are needed to confirm their safety profile.[46]

Question and Answer Session

Q. Prof Thaçi queried which are the main factors to consider regarding safety when choosing a treatment.

A. Prof Puig reiterated the need to assess the patient profile when choosing a treatment. For example, in the case of anti-TNFα agents, patients should be screened for serious infection, for example hepatitis B and *Mycobacterium tuberculosis*, and active infections should be monitored closely.

Q. Are you expecting that the safety of IL-23 inhibitors will be different to that of anti-TNFα agents, asked Prof Thaçi?

A. Prof Puig explained that in his opinion, IL-23 inhibitors are preferred in a patient with a history of active neoplasms due to the risk associated with IL-12 inhibitors and skin cancer, and the potential link between TNF dysregulation and cancer.

Q. Prof Thaçi asked, in a patient with a chronic syphilis infection, which treatment would you use?

A. I would use an IL-23p19 inhibitor, responded Prof Puig.

Q. Is *Candida* infection a fear particularly associated with treatment, asked Prof Thaçi?

A. *Candida* infection is bothersome but can be treated with fluconazole. The patient can be profiled (usually diabetic, obese, previous history of relapsing *Candida*, or female) and treated prophylactically, responded Prof Puig.

Q. Do TNFα inhibitors have a place in the future for short- or long-term management of psoriasis, as many centres are forced to use TNFα inhibitors or use them in psoriatic arthritis?

A. TNFα inhibitors have a place in healthy biologic naïve patients. Special consideration is required for patients with heart failure and advice from a cardiologist may be required, responded Prof Piaserico and Prof Puig.

Q. How are dosages up or downtitrated?

A. You can downtitrate by increasing the dose interval or lowering the dose of the drug if drug dosages are not fixed, explained Prof Piaserico.

Q. Do you expect higher rates of malignancies if you increase the dose of IL-23 inhibitors from 100 mg to 200 mg?

A. No, there is no dose-effect shown in clinical trials, confirmed Prof Puig.

Q. Prof Piaserico, do you screen for nonalcoholic fatty liver disease in daily practice?

A. We only screen patients for the purpose of clinical studies, responded Prof Piaserico. There are some data showing that IL-17 inhibition plays a major role in reducing the progression of nonalcoholic fatty liver disease.

Q. How would you screen a patient before prescribing an IL-23p19 inhibitor?

A. Prof Puig responded that he screens all patients before making a treatment decision. However, if he had only IL-23p19 inhibitors available, he would not screen at all.

Q. Do you think IL-23 inhibitors should become the first choice of biologics in the future?

A. The speakers agreed that treatment choice must be guided by efficacy, safety, cost, and local regulations.

Chairman's Closing Comments

Prof Thaçi presented the case of a 65-year-old woman who has been afflicted by psoriasis for several years. She does not have psoriatic arthritis but has diabetes and depression. Topical treatments and methotrexate have been ineffective. She has a previous history of malignancy (nonmelanoma skin cancer) and genital candidiasis. The audience were asked which treatment they would choose. The majority responded that they would use an IL-23 inhibitor. Prof Thaçi highlighted that this is a case-by-case decision and several treatment options are required to ensure tailored therapy, taking

the patient profile and patient's preference into account. In the case of psoriatic arthritis, it is important to consider consulting a rheumatologist. Prof Piaserico and Prof Puig advised that when switching biologics, they start the new biologic almost immediately. Prof Thaçi pointed out that it is important to consider side-effects or active infection when changing biologics.

WATCH THE FULL EADV SYMPOSIUM ON THE PSORIASIS ACADEMY ←

https://www.epgonline.org/psoriasis-academy/en/eadv-2019.html

References

1. Nestle FO et al. Psoriasis. N Engl J Med. 2009;361(5):496-509.
2. Nograles KE et al. IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. J Allergy Clin Immunol. 2009;123(6):1244-52.
3. Lowes MA et al. Pathogenesis and therapy of psoriasis. Nature. 2007;445(7130):866-73.
4. EPG Health. Psoriasis academy. 2019. Available at: https://www.epgonline.org/psoriasis-academy/en/treatment/systemic-and-biologic-treatments/biologic-treatments.html. Last accessed: 18 October 2019.
5. Slyepchenko A et al. T helper 17 cells may drive neuroprogression in major depressive disorder: proposal of an integrative model. Neurosci Biobehav Rev. 2016;64:83-100.
6. Fabbrini E et al. Association between specific adipose tissue CD4+ T-cell populations and insulin resistance in obese individuals. Gastroenterology. 2013;145(2):366-74.
7. Chen Y et al. Adipose tissue dendritic cells enhances inflammation by prompting the generation of Th17 cells. PLoS One. 2014;9(3):e92450.
8. Hatting M, Tacke F. From NAFLD to HCC: is IL-17 the crucial link? Hepatology. 2017;65(2):739-41.
9. Leung S et al. The cytokine milieu in the interplay of pathogenic Th1/Th17 cells and regulatory T cells in autoimmune disease. Cell Mol Immunol. 2010;7(3):182-9.
10. Wu X et al. Insight into non-pathogenic Th17 cells in autoimmune diseases. Front Immunol. 2018;9:1112.
11. Aschenbrenner D et al. An immunoregulatory and tissue-residency program modulated by c-MAF in human TH17 cells. Nat Immunol. 2018;19(10):1126-36.
12. Piaserico P. Mind the gap - the benefits of modern biologic treatment. Available at: https://www.epgonline.org/psoriasis-academy/en/eadv-2019/benefits-of-modern-biologic-treatment.html. Last accessed: 27 January 2020.
13. Whibley N, Gaffen SL. Gut-busters: IL-17 ain't afraid of no IL-23. Immunity. 2015;43(4):620-2.
14. Blauvelt A et al. IL-23/IL-17A dysfunction phenotypes inform possible clinical effects from anti-IL-17A therapies. J Invest Dermatol. 2015;135(8):1946-53.
15. Lories RJ, McInnes IB. Primed for inflammation: enthesis-resident T cells. Nat Med. 2012;18(7):1018-9.
16. Alcusky M et al. Dermatologist and patient preferences in choosing treatments for moderate to severe psoriasis. Dermatol Ther (Heidelb). 2017;7(4):463-83.
17. Reich K et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of two randomized Phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. Br J Dermatol. 2019. doi:10.1111/bjd.18232. [Epub ahead of print].
18. Thaçi D et al. Long-term efficacy of tildrakizumab in patients with moderate-to-severe psoriasis who were responders at Week 28: pooled analysis through 148 weeks from two Phase 3 trials. J Eur Acad Dermatol Venereol. 2019;33(Suppl 3):53.
19. Papp K et al. Adalimumab for moderate to severe chronic plaque psoriasis: efficacy and safety of retreatment and disease recurrence following withdrawal from therapy. Br J Dermatol. 2011;164(2):434-41.
20. van den Bemt BJ et al. Sustained effect after lowering high-dose infliximab in patients with rheumatoid arthritis: a prospective dose titration study. Ann Rheum Dis. 2008;67(12):1697-701.
21. Smolen JS et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet. 2013;381(9870):918-29.
22. Bongartz T et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295(19):2275-85.
23. Baniandrés O et al. Dose modification in biologic therapy for moderate to severe psoriasis: a descriptive analysis in a clinical practice setting. Actas Dermosifiliogr. 2015;106(7):569-77.
24. Romero-Jimenez RM et al. Efficiency of biological therapies in patients with moderate to severe psoriasis: impact of a pharmacotherapeutic protocol. J Dermatolog Treat. 2016;27(3):198-202.
25. Piaserico S et al. Down-titration of adalimumab and etanercept in psoriatic patients: a multicentre observational study. Acta Derm Venereol. 2016;96(2):251-2.
26. Sawyer LM et al. Assessing the relative efficacy of interleukin-17 and interleukin-23 targeted treatments for moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis of PASI response. PLoS One. 2019;14(8):e0220868.
27. Warren RB et al. Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015;135(11):2632-40.
28. Egeberg A et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. Br J Dermatol. 2018;178(2):509-19.
29. Armstrong AW et al. Improvement in patient-reported outcomes (Dermatology Life Quality Index and the Psoriasis Symptoms and Signs Diary) with guselkumab in moderate-to-severe plaque psoriasis: results from the Phase III VOYAGE 1 and VOYAGE 2 Studies. Am J Clin Dermatol. 2019;20(1):155-64.
30. Mrowietz U et al. Psoriasis: to treat or to manage? Exp Dermatol.

2014;23(10):705-9.

31. Teng MW et al. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. Nat Med. 2015;21(7):719-29.
32. Saleem MD et al. Relative versus absolute risk of comorbidities in patients with psoriasis. J Am Acad Dermatol. 2017;76(3):531-7.
33. Carretero G et al. Risk of adverse events in psoriasis patients receiving classic systemic drugs and biologics in a 5-year observational study of clinical practice: 2008-2013 results of the Biobadaderm registry. J Eur Acad Dermatol Venereol. 2015;29(1):156-63.
34. Medina C et al. Safety of classic and biologic systemic therapies for the treatment of psoriasis in elderly: an observational study from national BIOBADADERM registry. J Eur Acad Dermatol Venereol. 2015;29(5):858-64.
35. Dávila-Seijo P et al. Infections in moderate to severe psoriasis patients treated with biological drugs compared to classic systemic drugs: findings from the BIOBADADERM Registry. J Invest Dermatol. 2017;137(2):313-21.
36. Reich K et al. Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. Arch Dermatol Res. 2015;307(10):875-83.
37. Kalb RE et al. Risk of serious infection with biologic and systemic treatment of psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA Dermatol. 2015;151(9):961-9.
38. Fiorentino D et al. Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry. J Am Acad Dermatol. 2017;77(5):845-54.
39. Yiu ZZN et al. Risk of serious infections in patients with psoriasis on biologic therapies: a systematic review and meta-analysis. J Invest Dermatol. 2016;136(8):1584-91.
40. Asgari MM et al. Malignancy rates in a large cohort of patients with systemically treated psoriasis in a managed care population. J Am Acad Dermatol. 2017;76(4):632-8.
41. Dommasch ED et al. Risk of serious infection in patients receiving systemic medications for the treatment of psoriasis. JAMA Dermatol. 2019;155(10):1142-52.
42. Cui L et al. Efficacy and safety of biologics targeting IL-17 and IL-23 in the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis of randomized controlled trials. Int Immunopharmacol. 2018;62:46-58.
43. Erichsen CY et al. Biologic therapies targeting the interleukin (IL)-23/IL-17 immune axis for the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2019. doi:10.1111/jdv.15879. [Epub ahead of print].
44. Reich K et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a Phase 3, randomised controlled trial. Lancet. 2019;394(10201):831-9.
45. Gordon KB et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled Phase 3 trials. Lancet. 2018;392(10148):650-61.
46. Blauvelt A et al. Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials. Br J Dermatol. 2018;179(3):615-22.

Tildrakizumab in Patients with Moderate-to-Severe Psoriasis: Post-Hoc Analyses on Efficacy, Time to Relapse, Long-Term Safety in Elderly Population and Predictability From The reSURFACE 1 and reSURFACE 2 Phase III Clinical Trials

These posters were presented at the 28th European Academy of Dermatology and Venereology (EADV) Congress in Madrid, Spain, 9th–13th October 2019

Speakers: Kristen Reich,[1] Richard Warren,[2] Diamant Thaçi,[3] Peter van de Kerkhof[4]

1. Centre for Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Skinflammation® Center, Hamburg, and Dermatologikum Berlin, Germany
2. Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester NIHR Biomedical Research Centre, The University of Manchester, Manchester, UK
3. Institute and Comprehensive Centre for Inflammation Medicine, University of Lübeck, Lübeck, Germany
4. Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester NIHR Biomedical Research Centre, The University of Manchester, Manchester, UK

Disclosure: Prof Reich has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor, Covagen, Dermira, Eli Lilly, Forward Pharma, Fresenius Medical Care, Galapagos, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, Leo Pharma, Medac, Merck Sharp & Dohme, Miltenyi Biotec, Novartis, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant, Xenoport. Prof Warren has received research grants from AbbVie, Almirall, Amgen, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, and UCB; and consulting fees from AbbVie, Almirall, Amgen, Arena, Avillion, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, Sanofi, and UCB. Prof Thaçi has received honoraria or fees for serving on advisory boards, as a speaker, or as a consultant from AbbVie, Almirall, Bioskin, Boehringer Ingelheim, Celgene, Dignity, Eli Lilly, Galapagos, GlaxoSmithKline, Janssen Pharmaceutica, Leo Pharma, Medac, Merck Sharp & Dohme, Morphosys, Novartis, Pfizer, Regeneron, Samsung Sandoz-Hexal, Sanofi, Sun Pharmaceuticals, and UCB, and grants from Celgene and Novartis. Prof van de Kerkhof has received fees for consultancy service or lecturerships from AbbVie, Almirall, Amgen, Bristol Myers Squib, Celgene, Dermavant, Eli Lilly, Janssen Pharmaceutica, Leo Pharma, and Novartis.

Acknowledgements: Medical writing assistance was provided by Elizabeth Haygreen, Hyerange Medical Writing Ltd, Berkshire, UK.

Support: The publication of this article was funded by Almirall.

Citation: EMJ Dermatol. 2020;8[Suppl 2]:12-19.

Meeting Summary

Tildrakizumab is a monoclonal antibody with specificity for the p19 subunit of IL-23 that is approved for the treatment of moderate-to-severe plaque psoriasis in adults. Tildrakizumab was evaluated in two pivotal and parallel Phase III multicentre, double-blinded, randomised and placebo-controlled clinical trials: reSURFACE 1 and reSURFACE 2. These studies aimed to determine whether tildrakizumab is more effective than placebo and etanercept for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis. Four post-hoc analyses from the reSURFACE 1 and reSURFACE 2 Phase III clinical trials were presented at the 28th European Academy of Dermatology and Venereology (EADV) Congress 2019. These post-hoc analyses investigated: 1) time to relapse in patients who had stopped treatment with tildrakizumab; 2) whether early responses to tildrakizumab could predict later responses; 3) whether disease duration affected response to tildrakizumab; and 4) long-term safety in patients >65 years of age. Median time to relapse after stopping tildrakizumab treatment was shown to be 32–37 weeks after the last dose. Early response to tildrakizumab (at Weeks 4, 8, and 16) showed a high predictability of continued success in later weeks (Week 28). Compared to etanercept, patients' disease duration (≤5, >5 to ≤10, and >10 years) affected responses to tildrakizumab treatment less; however, patients receiving tildrakizumab who had a shorter disease duration at baseline did have higher efficacy rates at Week 28 than those who had longer disease durations before joining the studies. Lastly, up to Week 148, tildrakizumab was well-tolerated in patients >65 years of age.

INTRODUCTION

Psoriasis is a chronic, relapsing inflammatory skin disease, characterised in most cases by sharply demarcated, erythematous, pruritic plaques covered with silvery scales.[1] Dysregulation of the innate and adaptive cutaneous immune responses is responsible for the development and maintenance of psoriatic inflammation in skin, and includes the IL-23/Th17 inflammatory pathway.[1] The chronic nature of psoriasis necessitates long-term therapy, with mild-to-moderate psoriasis requiring topical treatment, and moderate-to-severe psoriasis usually requiring systemic treatment.[2] Biologics targeting specific inflammatory pathways have been developed for the treatment of plaque psoriasis and currently focus on cytokines involved in the development of the disease, including IL-23, IL-17A, and TNF-α.[1] IL-23, produced by dendritic cells, drives the expansion of Th17 cells and is a key cytokine in the development of psoriasis.[1] The first biologic targeting IL-23 to be approved for psoriasis treatment was ustekinumab, which binds the p40 subunit of IL-23.[1] However, as the p40 subunit of IL-23 is shared with IL-12, other immune mechanisms such as Th1 targeting are also affected by ustekinumab.[1] Therefore, development of newer biologics targeting IL-23 alone have focussed mainly on the p19 subunit, as it does not bind IL-12.[1] Three monoclonal antibodies with specificity for the p19 subunit of IL-23 have subsequently been developed and are either already approved or in clinical development: guselkumab, risankizumab, and tildrakizumab.[3-5]

Tildrakizumab, approved in 2018 for the treatment of adults with moderate-to-severe plaque psoriasis, was evaluated in two pivotal, parallel Phase III clinical trials: reSURFACE 1 and reSURFACE 2 and their long-term extension studies.[6,7] In this article, the results of four post-hoc analyses of reSURFACE 1 and reSURFACE 2 are shared, which investigated: 1) time to relapse in patients who had stopped treatment with tildrakizumab; 2) whether early responses to tildrakizumab could predict later responses; 3) whether disease duration affected response to tildrakizumab; and 4) long-term safety in patients >65 years of age. These analyses were presented as posters at the EADV congress 2019.

The reSURFACE 1 and reSURFACE 2 Phase III Trials

The reSURFACE 1 and reSURFACE 2 studies aimed to determine whether tildrakizumab is better than placebo and etanercept (a recombinant human fusion protein targeting TNF-α[8]) for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis.[6] In reSURFACE 1, 308 patients with moderate-to-severe psoriasis received 200 mg tildrakizumab,

309 received 100 mg tildrakizumab, and 155 received placebo (randomisation 2:2:1).[6] In the parallel reSURFACE 2 study, 314 patients received 200 mg tildrakizumab, 307 received 100 mg tildrakizumab, 156 received placebo, and 313 received etanercept (randomisation 2:2:1:2).[6] The studies were divided into three parts. Part 1 included Weeks 0–12, where patients were randomised as described above; Part 2 included Weeks 12–28, when patients who received placebo were rerandomised to receive 200 mg tildrakizumab or 100 mg tildrakizumab; and Part 3 included Weeks 28–64 for reSURFACE 1 and Weeks 28–52 for reSURFACE 2, when patients who responded to tildrakizumab were randomised (1:1) to either continue the same tildrakizumab dose or placebo (patients were retreated with the same tildrakizumab dose upon relapse).[6] Tildrakizumab was administered subcutaneously to patients in Weeks 0, 4, and 16. Efficacy of tildrakizumab was analysed using the following primary endpoints: the proportion of patients achieving a Psoriasis Area and Severity Index (PASI) 75 (≥75% improvement in PASI) and Physician's Global Assessment (PGA) response (score 0 or 1 with a reduction ≥2 degrees from baseline) at Week 12.[6]

The reSURFACE 1 and 2 trials included adults with moderate-to-severe plaque psoriasis affecting ≥10% body surface area, a PGA score of ≥3, and PASI ≥12. Baseline characteristics and demographics were similar across both studies and between the treatment arms.[6] In the two trials, patients receiving tildrakizumab showed significantly higher efficacy results (PASI 75) compared with placebo ($p<0.0001$ for both 100 mg and 200 mg tildrakizumab versus placebo) and etanercept ($p<0.0001$ for 200 mg tildrakizumab versus etanercept; $p=0.0010$ for 100 mg tildrakizumab versus etanercept).[6] At Week 12 of reSURFACE 1, 62% of the patients who received 200 mg tildrakizumab and 64% of patients who received 100 mg tildrakizumab achieved PASI 75, compared to 6% of patients in the placebo group.[6] Regarding the PGA response, 59% of the patients who received 200 mg tildrakizumab and 58% of the patients who received 100 mg tildrakizumab achieved the desired PGA response, compared to 7% of patients in the placebo group. At Week 12 of reSURFACE 2, 66% of the patients who received 200 mg tildrakizumab and 61% of patients who received 100 mg tildrakizumab achieved the primary endpoint of PASI 75, compared to 6% of patients in the placebo group and 48% of patients in the etanercept group. Regarding the PGA response, 59% of the patients who received 200 mg tildrakizumab and 59% of the patients who received 100 mg tildrakizumab group achieved a PGA response, compared to 4% of patients in the placebo group and 48% of patients in the etanercept group.[6]

Tildrakizumab was well-tolerated by patients in both studies.[6] The most common (≥1%) adverse effects included upper respiratory tract infections, injection site reactions, and diarrhoea.[6]

Post-Hoc Analysis of Time to Relapse in Patients Who Responded to Tildrakizumab Treatment in reSURFACE 1

Professor Kristen Reich

Long-term treatment is recommended for patients with psoriasis due to the chronic relapsing nature of the disease.[2] Time to relapse, relapse rates after discontinuation of treatment, as well as predictors of relapse are therefore important features of novel biologics for treatment of psoriasis.

A post-hoc analysis aimed to evaluate time to relapse in patients who had received tildrakizumab in Parts 1 and 2 of reSURFACE 1, who were classified as responders to tildrakizumab at the end of Part 2 (Week 28), and who were then randomised to receive placebo for Part 3 (Weeks 28–64).[9] The last dose of tildrakizumab these patients therefore received was at Week 16 and they were followed until the end of Part 3 of the study. In this post-hoc analysis, relapse was defined as loss of PASI 75 response between Weeks 28–64.[9]

At Week 28, 114 patients who were PASI 75 responders to 100 mg tildrakizumab and 119 patients who were PASI 75 responders to 200 mg tildrakizumab were randomised to receive placebo, with the option to be retreated with the same tildrakizumab dose upon relapse.[6,9] From Week 28, the median time to relapse was 20 weeks with 100 mg tildrakizumab and 25 weeks with 200 mg tildrakizumab (32–37 weeks since the last 100–200 mg tildrakizumab

dose).[9] Median time to loss of PASI 90 (≥90% improvement in PASI) response was between 16–20 weeks (28–32 weeks since the last 100–200 mg tildrakizumab dose).[9] A total of 20% of the patients who received 100 mg tildrakizumab and 24% of the patients who received 200 mg tildrakizumab did not relapse during the 36-week period (either they maintained PASI 75 or they were lost to follow up).[9] No rebound of disease was observed (defined as worsening of psoriasis over baseline value [PASI>125%], or new pustular, erythrodermic, or more inflammatory psoriasis occurring within 2 months of stopping therapy).[9]

Characteristics of the patients who relapsed were also analysed, and smoking status, BMI, disease duration at baseline, and length of time sustaining PASI 90 were shown to be good predictors of relapse.[9] Ex-smokers had 3.5-fold greater odds of relapse versus nonsmokers.[9] The odds of relapse was 6% higher for every 1-unit increase in BMI, 3% higher for every 1-year increase in disease duration, and 1% lower for every week sustaining a PASI 90 response before Week 28.[9]

Pooled Post-Hoc Analysis from reSURFACE 1 and reSURFACE 2 Demonstrates That Tildrakizumab Can Provide an Early Predictability of Response

Professor Richard Warren

Response-guided therapy, particularly at early timepoints, is clinically useful for psoriasis treatment with biologics and can help guide better treatment decisions for patients. A pooled post-hoc analysis from reSURFACE 1 and reSURFACE 2 aimed to evaluate whether an early response to tildrakizumab at Weeks 4, 8, and 16 (PASI 50 response [≥50% improvement in PASI]) could predict a later response at Week 28, defined as either a PASI 90 response or an absolute PASI of <3.[10]

A total of 593 patients who received 100 mg tildrakizumab and 597 patients who received 200 mg tildrakizumab were analysed.[10] PASI 50 was achieved by 40.0% and 39.0% of the patients who received 100 mg and 200 mg tildrakizumab, respectively, by Week 4; by 74.8% and 76.4% of patients who received 100 mg and 200 mg tildrakizumab, respectively, by Week 8; and, by 88.3% and 90.6% of patients who received 100 mg and 200 mg tildrakizumab, respectively, by Week 16.[10]

Response to tildrakizumab at earlier weeks showed a high predictability of continued success in later weeks.[10] For those patients who achieved a PASI 50 at Week 4, 66.7% (100 mg tildrakizumab) and 74.4% (200 mg tildrakizumab) achieved a PASI 90 response and 77.1% (100 mg tildrakizumab) and 84.8% (200 mg tildrakizumab) achieved a PASI <3 at Week 28.[10] For those patients who achieved a PASI 50 at Week 8, 64.4% (100 mg tildrakizumab) and 70.2% (200 mg tildrakizumab) achieved a PASI 90 response and 77.1% (100 mg tildrakizumab) and 80.9% (200 mg tildrakizumab) achieved a PASI <3 at Week 28.[10] For those patients who achieved a PASI 50 at Week 16, 60.6% (100 mg tildrakizumab) and 64.2% (200 mg tildrakizumab) achieved a PASI 90 response and 73.1% (100 mg tildrakizumab) and 76.0% (200 mg tildrakizumab) achieved a PASI <3 at Week 28 (Figure 1).[10] Additionally, lack of response to tildrakizumab by Weeks 8 and 16 was highly predictive of continued lack of response at Week 28.[10] Patients who had not achieved PASI 50 response at Week 8 were unlikely to achieve PASI 90 response at Week 28; the corresponding rates were 21.8% (100 mg tildrakizumab) and 21.6% (200 mg tildrakizumab). Similarly, only 29.9% (100 mg tildrakizumab) and 33.6% (200 mg tildrakizumab) had PASI values <3 at Week 28.[10] For patients who did not achieve PASI 50 response at Week 16, the corresponding response rates were 0.0% (regardless of dose) for PASI 90 at Week 28, and 14.5% (100 mg tildrakizumab) and 13.8% (200 mg tildrakizumab) for PASI <3 at Week 28.[10]

However, failure to achieve a PASI 50 by Week 4 did not necessarily predict a continued lack of response: of those patients who did not achieve a response at Week 4, 44.9% (100 mg tildrakizumab) and 47.9% (200 mg tildrakizumab) achieved a PASI 90 response at Week 28; the corresponding rates for PASI <3 were 57.1% (100 mg tildrakizumab) and 59.5% (200 mg tildrakizumab) (Figure 2).[10]

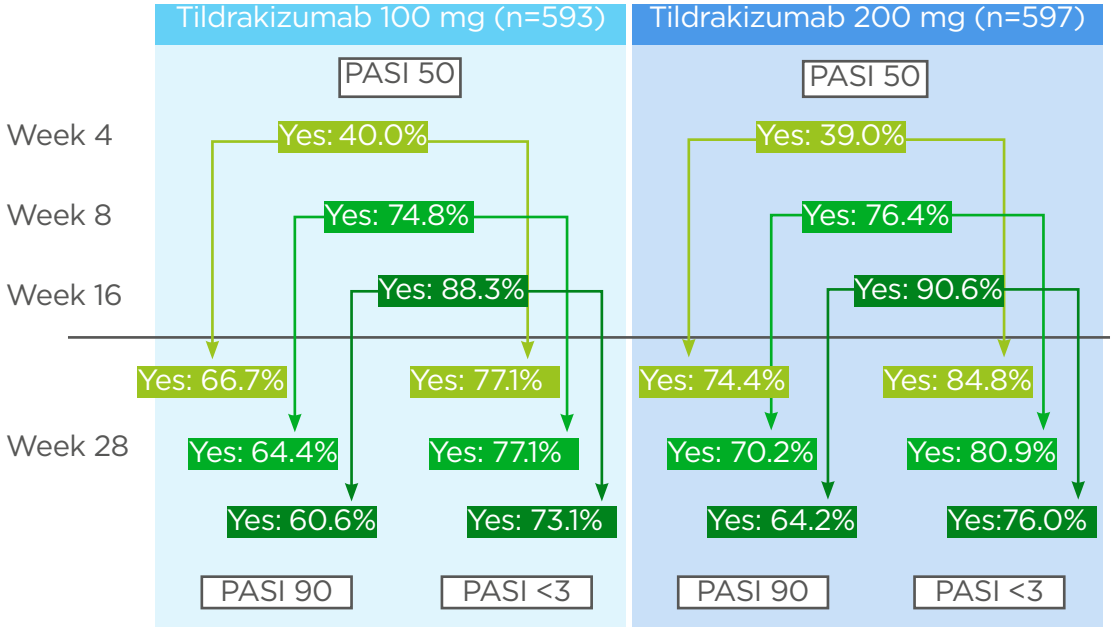


Figure 1: Patients with PASI 90 response or Psoriasis Area and Severity Index (PASI) <3 at Week 28 when PASI 50 was achieved at Weeks 4, 8, and 16.[9]

PASI: Psoriasis Area and Severity Index.

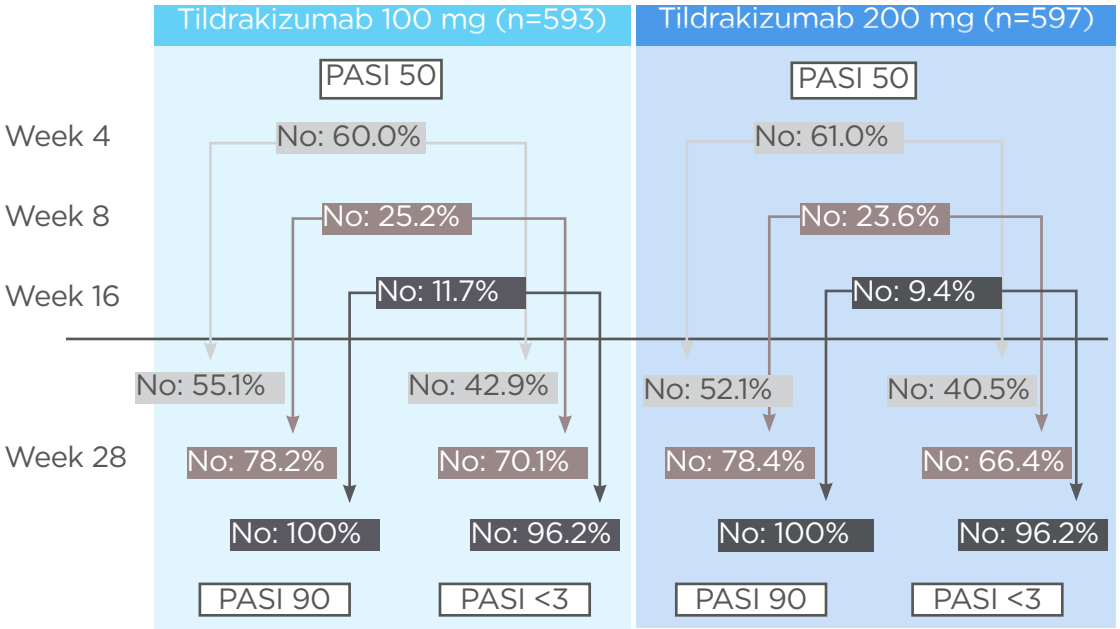


Figure 2: Patients without Psoriasis Area and Severity Index (PASI) 90 response or PASI <3 at Week 28 when PASI 50 was not achieved at Weeks 4, 8, and 16.[9]

PASI: Psoriasis Area and Severity Index.

Efficacy of Tildrakizumab According to Disease Duration at Baseline in a Pooled Post-Hoc analysis from reSURFACE 1 and reSURFACE 2

Professor Diamant Thaçi

The length of time patients have experienced psoriasis disease can affect their responses to certain biological treatments.[11] A pooled post-hoc analysis from reSURFACE 1 and reSURFACE 2 therefore aimed to investigate whether disease duration (≤5, >5 to ≤10, and >10 years) at baseline affected patient responses to tildrakizumab.[12] Response to tildrakizumab was determined by efficacy at Week 28: proportions of patients achieving PASI 75, PASI 90, and an absolute PASI <3.[12] A total of 1,479 patients were included in this analysis: 273 patients with a disease duration ≤5 years, 266 patients with >5 to ≤10 years, and 940 patients with >10 years.[12] Data from this post-hoc analysis are based on the full analysis set; missing data were handled using nonresponder imputation.[12]

Overall, compared to etanercept, patients receiving tildrakizumab demonstrated less difference between efficacy endpoints based on disease duration; however, patients treated with tildrakizumab who had experienced shorter disease duration did have higher efficacy rates than patients who had experienced longer disease durations.[12] For patients receiving 100 mg tildrakizumab, at Week 28, PASI 75 was achieved in 81.2% (≤5 years disease duration), 76.4% (>5 to ≤10 years), and 72.6% (>10 years) of patients; PASI 90 was achieved in 61.5% (≤5 years), 53.8% (>5 to ≤10 years), and 48.2% (>10 years) of patients; and PASI <3 was achieved in 72.1% (≤5 years), 60.4% (>5 to ≤10 years), and 60.8% (>10 years) of patients.[12]

For patients receiving 200 mg tildrakizumab at Week 28, PASI 75 was achieved in 83.3% (≤5 years disease duration), 71.2% (>5 to ≤10 years), and 74.9% (>10 years) of patients; PASI 90 was achieved in 67.6% (≤5 years), 53.3% (>5 to ≤10 years), and 54.7% (>10 years) of patients; and PASI <3 was achieved in 74.1% (≤5 years), 65.4% (>5 to ≤10 years), and 66.2% (>10 years) of patients.[12]

For patients receiving etanercept at Week 28, PASI 75 was achieved in 60.5% (≤5 years disease duration), 45.3% (>5 to ≤10 years), and 54.4% (>10 years) of patients; PASI 90 was achieved in 46.5% (≤5 years), 24.5% (>5 to ≤10 years), and 26.9% (>10 years) of patients; and PASI <3 was achieved in 55.8% (≤5 years), 39.6% (>5 to ≤10 years), and 39.4% (>10 years) of patients.[12]

Pooled Post-Hoc Analysis from reSURFACE 1 and reSURFACE 2 Investigates Long-Term Safety of Tildrakizumab in Patients 65 Years of Age or Older

Professor Peter van de Kerkhof

Patients with psoriasis who are >65 years of age are more likely to suffer comorbidities and to develop adverse effects because of treatment than younger patients.[13] A pooled post-hoc analysis from reSURFACE 1 and reSURFACE 2 therefore aimed to consider the long-term safety profile of tildrakizumab in patients who were >65 years of age.[14] A total of 161 patients >65 years of age were exposed to tildrakizumab up to Week 148 (159.5 patient years [PY] of exposure to 100 mg tildrakizumab and 170.8 PY of exposure to 200 mg tildrakizumab).[14] PY of exposure to etanercept was 14.7.[14]

Up to Week 148, tildrakizumab was well-tolerated in patients older than 65 years of age, with low drug-related serious adverse events and adverse events of special interest.[14] In addition, no dose-related increase in the rate of adverse events was observed.[14] The exposure adjusted incidence rates (EAIR; events per 100 PY of exposure) of drug-related serious adverse events were 2.51, 1.76, and 6.83 for patients receiving 100 mg tildrakizumab, 200 mg tildrakizumab, and etanercept, respectively.[14] The EAIR of severe infections were 3.76, 2.34, and 6.83 for patients receiving 100 mg tildrakizumab, 200 mg tildrakizumab, and etanercept, respectively.[14] The EAIR of malignancies (excluding nonmelanoma skin cancer) were 1.88, 1.76, and 6.83 for patients receiving 100 mg tildrakizumab, 200 mg tildrakizumab and etanercept, respectively.[14] The EAIR of confirmed extended major adverse cardiovascular events (nonfatal

myocardial infarction, non-fatal stroke, unstable angina, coronary revascularisation, resuscitated cardiac arrest, and cardiovascular deaths that were confirmed as "cardiovascular" or "sudden") were 0.63, 1.17, and 6.83 for patients receiving 100 mg tildrakizumab, 200 mg tildrakizumab, and etanercept, respectively.[14] Finally, the EAIR of injection site reactions were 0.63, 2.34, and 20.48 for patients receiving 100 mg tildrakizumab, 200 mg tildrakizumab, and etanercept, respectively.[14]

SUMMARY AND CONCLUSIONS

Tildrakizumab was approved in Europe and the USA in 2018 for the treatment of adults with moderate-to-severe plaque psoriasis.[5,15] Two pivotal Phase III studies, reSURFACE 1 and reSURFACE 2, showed that tildrakizumab was efficacious and significantly more effective than placebo ($p<0.0001$ for both 100 mg and 200 mg tildrakizumab versus placebo) and etanercept ($p<0.0001$ for 200 mg tildrakizumab versus etanercept; $p=0.0010$ for 100 mg tildrakizumab versus etanercept), with a favourable safety profile.[6] Four post-hoc analyses from reSURFACE 1 and reSURFACE 2 described here expand these results and provide more information on the clinical use of tildrakizumab.

Reich et al.[9] showed that the median time to relapse after stopping tildrakizumab treatment was 32–37 weeks since the last dose, and that smoking status, BMI, disease duration, and length of time sustaining PASI 90 were good predictors of relapse. These data can help inform decisions about length of time patients continue to receive treatment and whether it is possible to stop treatment at any time.

Warren et al. demonstrated that early response to tildrakizumab (at Weeks 4, 8, and 16) showed a high predictability of continued success in later weeks (Week 28). Conversely, a lack of response by Weeks 8 and 16 predicted a continued lack of response; however, it is important to note that failure to achieve a response by Week 4 did not necessarily predict a continued lack of response. These data could be very useful in cost-effectiveness models and in clinical practice to help guide better treatment decisions for patients.[10]

Thaçi et al.[12] showed that, compared to etanercept, disease duration at baseline affected responses to tildrakizumab treatment less; however, patients treated with tildrakizumab who had experienced shorter disease duration did have higher efficacy rates (PASI 75, PASI 90, and an absolute PASI <3 at Week 28) than those who had experienced longer disease durations. These data suggest that treating as early as possible might be beneficial for patients. However, further analysis could include other baseline characteristics such as failure on previous biologic use, as this could influence response rates and may be higher in patients with longer disease duration at baseline.

Lastly, van de Kerkhof et al.[14] demonstrated that up to Week 148, tildrakizumab was well-tolerated in patients older than 65 years of age. As many patients with psoriasis are in this age group and may experience comorbidities, this data is helpful for informing treatment decisions for this age group.

In summary, these post-hoc analyses from the reSURFACE 1 and reSURFACE 2 studies provide key information that will help inform tildrakizumab treatment decisions for both clinicians and patients.

References

1. Rendon A, Schäkel K. Psoriasis pathogenesis and treatment. Int J Mol Sci. 2019;20(6):E1475.
2. Nast A et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris - Update 2015 - Short version - EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015;29(12): 2277-94.
3. Electronic Medicines Compendium. Tremfya 100 mg solution for injection in pre-filled pen. Available at: https://www.medicines.org.uk/emc/product/9587/smpc. Last accessed: 21 October 2019.
4. European Medicines Agency. Summary of opinion (initial authorisation): Skyrizi risankizumab. Available at: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-skyrizi_en.pdf. Last accessed: 21 October 2019.
5. Electronic Medicines Compendium. Ilumetri 100 mg solution for injection in pre-filled syringe. Available at:

https://www.medicines.org.uk/emc/product/9819/smpc. Last accessed 21st October 2019.

6. Reich K et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): Results from two randomised controlled, phase 3 trials. Lancet. 2017;390(10091):276-88.
7. Reich K et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of two randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. Br J Dermatol. 2019. doi: 10.1111/bjd.18232. [Epub ahead of print].
8. Electronic Medicines Compendium. Enbrel 25 mg powder and solvent for solution for injection. Available at: https://www.medicines.org.uk/emc/medicine/3343. Last accessed. 21 October 2019.
9. Reich K et al. Time to relapse in patients with moderate-to-severe psoriasis who were tildrakizumab responders at week 28: Post-hoc analysis through 64 weeks from reSURFACE 1 trial. Abstract P1697. EADV Congress, Madrid, Spain, 9-13 October 2019.
10. Warren RB et al. Tildrakizumab provides early predictability of response in patients with moderate-to-severe psoriasis: Results from reSURFACE 1 and reSURFACE 2 phase 3 trials. Abstract P1692. EADV Congress, Madrid, Spain, 9-13 October 2019.
11. Edson-Heredia E et al. Heterogeneity of response to biologic treatment: Perspective for psoriasis. J Invest Dermatol. 2014;134(1):18-23.
12. Thaçi D et al. Efficacy of tildrakizumab in patients with moderate-to-severe psoriasis according to disease duration: Pooled analysis from reSURFACE 1 and reSURFACE 2 phase 3 trials at week 28. Abstract P1754. EADV Congress, Madrid, Spain, 9-13 October 2019.
13. Fernandez-Torres et al. Psoriasis in patients older than 65 years. A comparative study with younger adult psoriatic patients. J Nutr Health Aging. 2012;16(6):586-91.
14. Van der Kerkhof PC et al. Long-term safety of tildrakizumab in patients 65 years of age or older with moderate to severe psoriasis: pooled analysis through 3 years (148 weeks) from reSURFACE 1 and reSURFACE 2 phase 3 trials. Abstract P1731. EADV Congress, Madrid, Spain, 9-13 October 2019.
15. HCPLive® Network. FDA approves tildrakizumab for certain plaque psoriasis patients. Available at: https://www.mdmag.com/medical-news/fda-approves-tildrakizumab-for-certain-plaque-psoriasis-patients. Last accessed: 21 October 2019.

Long-Term Safety of Tildrakizumab in Patients with Moderate-to-Severe Plaque Psoriasis through 3 Years (148 Weeks) from reSURFACE 1 and reSURFACE 2 Phase III Trials

Two posters and an oral presentation were presented at the 24th World Congress of Dermatology (WCD), Milan, held from 10th to 15th June 2019 in Milan, Italy

Speakers: Kristian Reich,[1] Diamant Thaçi,[2] Lars Iversen,[3] Ignasi Pau-Charles[4]

1. Centre for Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Skinflammation® Center, Hamburg, Germany
2. Institute and Comprehensive Centre for Inflammation Medicine, University of Lübeck, Lübeck, Germany
3. Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark
4. Almirall R&D, Barcelona, Spain

Disclosure: Dr Reich has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Covagen, Forward Pharma, Fresenius Medical Care, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Merck Sharp & Dohme, Novartis, Miltenyi Biotec, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Takeda, UCB, Valeant, and Xenoport. Prof Thaçi has received honoraria or fees for serving on advisory boards, as a speaker, or as a consultant from AbbVie, Almirall, Bioskin, Boehringer Ingelheim, Celgene, Dignity, Eli Lilly, Galapagos, GlaxoSmithKline, Janssen Pharmaceutica, Leo Pharma, Medac, Merck Sharp & Dohme, Morphosys, Novartis, Pfizer, Regeneron, Samsung Sandoz-Hexal, Sanofi, Sun Pharmaceuticals, and UCB; and grants from Celgene and Novartis. Dr Iversen has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Astra Zeneca, BMS, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Janssen-Cilag, Kyowa, Leo Pharma, MSD, Novartis, Pfizer, and UCB. Dr Pau-Charles is an employee of Almirall S.A.

Acknowledgements: Writing assistance was provided by Dr Eleanor Roberts, Beeline Science Communications Ltd, London, UK.

Support: The publication of this article was funded by Almirall. The views and opinions are those of the authors and not necessarily those of Almirall.

Citation: EMJ Dermatol. 2020;8[Suppl 2]:20-25

Meeting Summary

IL-23 plays a key regulatory role in psoriasis, and the high-affinity anti-IL-23p19 monoclonal antibody tildrakizumab is effective for the treatment of adults with moderate-to-severe plaque psoriasis. At the meeting, two posters and an oral presentation explored the safety of tildrakizumab up to 148 weeks, including analyses of extended major adverse cardiovascular events (MACE), severe infections, and malignancies. Safety was assessed over extension periods of two Phase III, double-blinded, three-

part, parallel group, randomised, placebo-controlled trials: reSURFACE 1 (N=772) and reSURFACE 2 (N=1,090) in adults with moderate-to-severe plaque psoriasis. Treatment switching occurred during the trial and the number of patients taking each treatment were 200 mg tildrakizumab (TIL 200; n=928), 100 mg tildrakizumab (TIL 100; n=872), placebo (n=543), or etanercept (reSURFACE 2 only) (n=313). Exposure-adjusted incidence rates (EAIR) (all preferred terms) are reported: any event ≥0.10 events/100 patient-years of exposure for severe infections; events/100 patient-years of exposure for MACE and malignancies. EAIR for MACE with TIL 200, TIL 100, etanercept, and placebo were 0.54, 0.40, 0.65, and 0.49, respectively. For severe infections, these were 1.12 (TIL 200), 1.14 (TIL 100), 1.96 (etanercept), and 0.97 (placebo). EAIR for malignancies, excluding non-melanoma skin cancer (NMSC), were 0.39, 0.55, 1.30, and 0.00 for TIL 200, TIL 100, etanercept, and placebo groups, respectively. For NMSC, respective EAIR were 0.49, 0.50, 1.30, and 0.97. In conclusion, in adults with moderate-to-severe plaque psoriasis there were low rates of MACE, severe infections, and malignancies in participants who had taken tildrakizumab over 148 weeks, comparable to the rates for etanercept and placebo.

Overview

IL-23 plays a key regulatory role in the pathogenesis of plaque psoriasis and medications targeting IL-23 have been shown to be effective for people with this skin condition.[1-6] Tildrakizumab is a high-affinity, anti-IL-23p19 monoclonal antibody approved for treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy.[1]

Trials showing efficacy and safety[1,2,7] of tildrakizumab up to 64 weeks have been published, and long-term trials have been carried out for up to 3 years. The oral presentation and two posters detailed at the meeting explored several safety aspects of tildrakizumab over 148 weeks, including analyses of confirmed extended MACE, severe infections, and malignancies.

Study Design

Tildrakizumab safety and efficacy were assessed following the initial study and extension periods of two Phase III, double-blinded, three-part, parallel-group, randomised, placebo-controlled trials: reSURFACE 1 and reSURFACE 2 (Figure 1). Extension period efficacy results are not discussed here. These studies took place over numerous sites, including hospital dermatology units, speciality clinics, private practices, and research centres in several European countries, North America, Australasia, and Asia.[1,2]

In Part 1, adults with moderate-to-severe plaque psoriasis were randomised to TIL 200, TIL 100, a placebo, or etanercept (reSURFACE 2 only) (Figure 1). In Part 2, the placebo arm was switched to TIL 100 or TIL 200 after Week 12. From Week 28, treatment in Part 3 was determined based on treatment in the previous arms and treatment response as assessed by Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA) scores[1,2] (Figure 1). Etanercept responders were discontinued in Part 3; non or partial responders (PASI ≥50) were switched to TIL 200.

Overall participant numbers in the trials were 772 in reSURFACE 1 and 1,090 in reSURFACE 2.[1,2] For the analysis, each group included those who received treatment in at least one part of the study. Some participants were switched between treatments during the trials and they received more than one treatment; therefore, the numbers in each treatment group are higher than the participant numbers. Treatment group numbers were 928 (TIL 200), 872 (TIL 100), 313 (etanercept), and 543 (placebo). Total patient-years of follow-up were 2,046.71 (TIL 200), 2,014.49 (TIL 100), 153.42 (etanercept), and 205.30 (placebo). An adverse event (AE) was assigned to the treatment taken at the time the AE occurred, e.g., if an AE happened while a participant was in a TIL group, the AE was assigned to this group, even if they had initially received etanercept.

Groups were well balanced according to baseline characteristics that were considered reasonably standard for this population. Mean age ranged from 45.7 to 46.6 years (standard deviation: 12.6–14.0), mean weight ranged from 88.0 to 89.1 kg (21.5–23.6), and the majority in all groups were male (70–72%). Mean PASI and mean affected body surface area scores were also similar, ranging from 19.8 to 20.2 (7.4–7.9) and 29.8 to 31.8% (16.6–17.8), respectively.

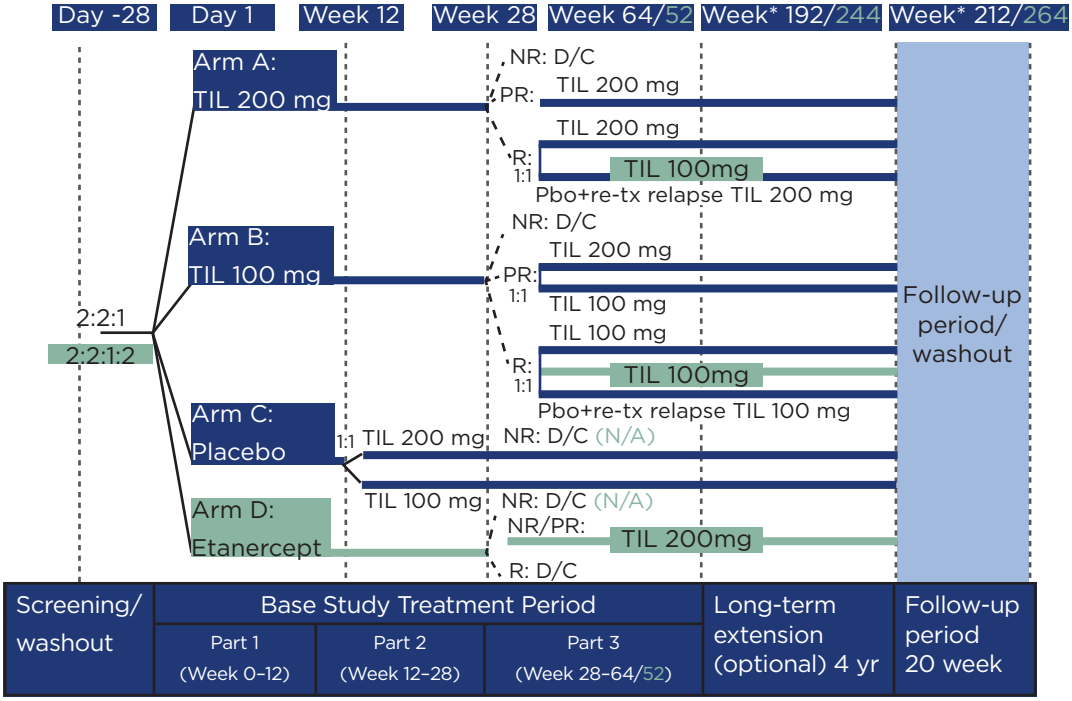


Figure 1: Study design.

Differences in design for reSURFACE 2 versus reSURFACE 1 are shown in turquoise. *Wk 192/212 is starting at extension Week 0.

D/C: discontinued; N/A: not applicable; NR: non-responders; Pbo: placebo; PR: partial responders; R: responders; TIL: tildrakizumab; tx; treatment.

Adapted from Reich et al.[1]

For severe infections, EAIR of any event ≥0.10 events per 100 patient-years of exposure were reported. For MACE and malignancies, events/100 patient-years of exposure were reported (Table 1).

Incidence of Confirmed Extended Major Adverse Cardiovascular Events

Oral Presentation by Doctor Ignasi Pau-Charles (lead Author: Doctor Lars Iversen)

People with psoriasis are at increased risk of cardiovascular events (CE).[8-10] While the usual definition of major CE includes only non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths, in this analysis 'extended MACE' also included unstable angina, coronary revascularisation, resuscitated cardiac arrest, and cardiovascular deaths confirmed as 'cardiovascular' or 'sudden'. Deaths and serious CE were adjudicated by an external clinical committee.

Notably, around 25% of the participants had a history of at least one CE or disease and the most prevalent risk factor was hypertension, occurring in 26.0–28.1% of the participants. Other risk factors included hypercholesterolaemia, hyperlipidaemia, obesity, and Type 2 diabetes mellitus, all with prevalences of 4–8%, with a lower prevalence of hypertriglyceridaemia (0.6%).

In the TIL 200 and TIL 100 groups, there were 0.54 and 0.40 events of confirmed extended MACE per 100 patient years, respectively (i.e., EAIR) (see Table 1 for incidences and 95% confidence intervals [CI]). The events with the highest EAIR were coronary artery disease (EAIR: 0.20; CI: 0.0–0.39/four events in the TIL 200 group) and acute myocardial infarction (EAIR: 0.15; CI: 0.00–0.32/3 in the TIL 200 group, EAIR: 0.50; CI: 0.00–15/1 in the TIL 100 group).

Table 1: Exposure-adjusted incidence rates (all preferred terms).

	TIL 200 (n=928)	TIL 100 (n=872)	ETN (n=313)	PBO (n=543)
	n, EAIR (95% confidence interval)			
Confirmed extended MACE	11 0.54 (0.21–0.86)	8 0.40 (0.12–0.68)	1 0.65 (0.0–1.96)	1 0.49 (0.0–1.46)
Severe infections	23 1.12 (0.66–1.59)	23 1.14 (0.67–1.62)	3 1.96 (0.0–4.21)	2 0.97 (0.0–2.35)
Malignancies excluding NMSC	8 0.39 (0.11–0.67)	11 0.55 (0.22–0.88)	2 1.30 (0.0–3.15)	0
NMSC	10 0.49 (0.18–0.80)	10 0.50 (0.18–0.81)	2 1.30 (0.0–3.15)	2 0.97 (0.0–2.35)

Data are n, events per 100 patient-years of exposure (95% confidence interval) for MACE and malignancies (NMSC and non-NMSC). Severe infections were considered ≥0.10 events per 100 patient-years of exposure (95% confidence interval).

EAIR: exposure-adjusted incidence rates; ETN: etanercept; MACE: major adverse cardiovascular event; NMSC: non-melanoma skin cancer; PBO: placebo; TIL: tildrakizumab.

The EAIR was 0.05 (CI: 0.00–0.15/1) with TIL 200 for aneurysm, angina pectoris, coronary artery stenosis, myocardial infarction, and transient ischaemic attack, and with TIL 100 for angina pectoris, cerebral haemorrhage, cerebral infarction, cardiovascular accident, death, myocardial infarction, respiratory arrest, and thrombotic cerebral infarction. There was one reported case of MACE each in the etanercept and placebo groups (coronary artery stenosis, EAIR: 0.65; CI: 0.00–1.96, and cerebellar infarction, EAIR: 0.49; CI: 0.00–1.46, respectively), meaning the overall EAIR in both groups were comparable to those in the TIL groups (Table 1).

Four deaths were recorded, all in those with a history of cardiovascular risk factors. These included single cases of aneurysm (TIL 200), myocardial infarction (TIL 100), and respiratory arrest (TIL 100), and one (recorded as 'death') that was a presumed myocardial infarction (TIL 100), but with no further details provided. All were adjudicated as unrelated to study medication.

In conclusion, compared to both etanercept and placebo, tildrakizumab has a favourable long-term safety profile regarding confirmed extended MACE.

Incidence of Severe Infections

Poster Presented by Professor Diamant Thaçi (Poster No: 1954)

Some immune system-targeting therapies have been associated with severe infections,[11-13] making it important to monitor over time. Here, severe infections were defined as any infection meeting the regulatory definition of a serious AE (SAE) or requiring intravenous antibiotics, irrespective of whether it was deemed a SAE.[7]

Overall, there was an EAIR of severe infections of 1.14 in the TIL 100 group and 1.12 in the TIL 200 group, with a higher value of 1.96 for the etanercept group and a slightly lower one of 0.97 for the placebo group (Table 1). Most commonly reported severe infections with TIL 200 were cellulitis (EAIR: 0.20; CI: 0.00–0.39/4), diverticulitis and pneumonia (both EAIR: 0.15; CI: 0.00–0.32/3), with an EAIR of 0.05 (CI: 0.00–0.15/1) for the following: appendicitis, gastroenteritis, herpes zoster, and wound infection. With TIL 100, the most commonly reported severe infections were appendicitis, cellulitis, diverticulitis, gastroenteritis, and sinusitis (all EAIR: 0.15; CI: 0.00–0.32/3), with an EAIR of 0.10 (CI: 0.00–

0.24/2) for wound infection and 0.05 (CI: 0.00–0.15/1) for pneumonia. In the etanercept group, cellulitis, herpes zoster, and urosepsis all had EAIR of 0.65 (CI: 0.00–1.96/1), with an EAIR for cellulitis of 0.97 (CI: 0.00–2.35/2) in the placebo group.

These data indicate that the risk of severe infection is low in patients with moderate-to-severe plaque psoriasis being treated long term with tildrakizumab.

Incidence of Malignancies

Poster Presented by Doctor Kristian Reich (Poster No: 1975)

There is an increased risk of certain malignancies, including NMSC, in individuals with psoriasis.[14] In these studies, the EAIR for malignancies (excluding NMSC) was highest in the etanercept group (1.30), with lower rates of 0.55 and 0.39 in the TIL 100 and TIL 200 groups, respectively. There were no malignancies reported in the placebo group (Table 1).

For TIL 200, the most frequent malignancy was pancreatic cancer (EAIR: 0.10; CI: 0.00–0.24/2). In both TIL groups, bladder transitional cell carcinoma, breast cancer, papillary thyroid cancer, and rectal adenocarcinoma had EAIR of 0.05 (CI: 0.00–0.15/1) , with the same values for metastatic breast cancer and prostate cancer in the TIL 200 group and for acute myeloid leukaemia, diffuse large B-cell carcinoma, leiomyosarcoma, malignant melanoma *in situ*, non-Hodgkin's lymphoma, ovarian cancer, and thyroid cancer in the TIL 100 group. In the etanercept group, EAIR were 0.65 (CI: 0.00–1.96/1) for both breast cancer and lung adenocarcinoma.

The highest EAIR for NMSC was 1.30 in the etanercept group. The EAIR in the other groups were placebo (0.97), TIL 100 (0.50), and TIL 200 (0.49) (Table 1). The most frequent NMSC was basal cell carcinoma, with EAIR of 0.34 (CI: 0.08–0.60/7) with TIL 200, 0.30 (CI: 0.05–0.54/6) with TIL 100, 1.30 (CI: 0.00–3.15/2) with etanercept, and 0.49 (CI: 0.00–1.46/1) with the placebo. The second most frequent NMSC was squamous cell carcinoma of the skin: TIL 200: 2.0 (CI: 0.00–0.24/2); TIL 100: 0.15 (CI: 0.00–0.32/3); placebo: 0.49 (CI: 0.00–1.46/1). Bowen's disease occurred with an EAIR of 0.05 (CI: 0.00–0.15/1) in the TIL 200 group and 0.10 (CI: 0.00–0.24/2) in the TIL 100 group, with an EAIR of 0.05 (CI: 0.00–0.15/1) for squamous cell carcinoma *in situ* of the skin in the TIL 100 group.

Compared to etanercept and placebo, both 100 mg and 200 mg doses of tildrakizumab demonstrated low rates of malignancies over time.

CONCLUSION

Efficacy trials of tildrakizumab following 52 weeks use show PASI ≥75 was maintained in >85% of those who initially responded to tildrakizumab 100 mg or 200 mg by 16 weeks.[2] Here, low incidence rates of MACE, severe infections, and malignancies were observed in individuals with moderate-to-severe plaque psoriasis administered tildrakizumab for up to 148 weeks, comparable to rates for individuals treated with either etanercept or placebo. As such, the long-term safety profile of tildrakizumab is favourable.

References

1. Reich K et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, Phase III trials. Lancet. 2017;390(10091):276-88.
2. Papp K et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a Phase IIb randomised placebo-controlled trial. Br J Dermatol. 2015;173(4):930-9.
3. Blauvelt A et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate-to-severe psoriasis: results from the Phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017;76(3):405-17.
4. Reich K et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate-to-severe psoriasis with randomised withdrawal and retreatment: results from the Phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol. 2017;76(3):418-31.
5. Krueger JG et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomised, double-blind, placebo-

controlled trial. J Allergy Clin Immunol. 2015;136(1):116-24.

6. Papp KA et al. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. N Engl J Med. 2017;376(16):1551-60.
7. Blauvelt A et al. Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials. Br J Dermatol. 2018;179(3):615-22.
8. Armstrong EJ et al. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc. 2013;2(2):e000062.
9. Mehta NN et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. Am J Med. 2011;124(8):775.e1–6.
10. Ogdie A et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. Ann Rheum Dis. 2015;74(2):326-32.
11. Hueber W et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo controlled trial. Gut. 2012;61(12):1693-700.
12. Strober B et al. Short- and long-term safety outcomes with ixekizumab from 7 clinical trials in psoriasis: etanercept comparisons and integrated data. J Am Acad Dermatol. 2017;76(3):432-40.
13. van de Kerkhof PCM et al. Secukinumab long-term safety experience: a pooled analysis of 10 Phase II and III clinical studies in patients with moderate to severe plaque psoriasis. J Am Acad Dermatol. 2016;75(1):83-98.
14. Kimball AB et al. Incidence rates of malignancies and hospitalised infectious events in patients with psoriasis with or without treatment and a general population in the U.S.A.: 2005–09. Br J Dermatol. 2014;170(2):366-73.