

The dangers of undertreatment in paediatric psoriasis

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Disclosures

- ▶ Has received grants from/was involved in clinical trials from Abbvie, Celgene, Eli Lilly, Janssen, Leo Pharma and Pfizer
- ▶ Served as a consultant for Abbvie, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer and UCB; fees were paid directly to the institution

Treatment of paediatric psoriasis: a challenge

- ▶ Many treatments still off label
- ▶ Unknown long-term efficacy
- ▶ Unknown long-term safety
- ▶ More often facial psoriasis than adults
- ▶ Psoriasis can negatively influence course of life



Treatment choices¹

- ▶ Age
- ▶ Severity
- ▶ Current and prior treatments
- ▶ Practicality of the regimen
- ▶ Costs and accessibility
- ▶ Patient's preferences
- ▶ Efficacy & safety of treatment
- ▶ Effect on quality of life
- ▶ Comorbidities

Shift in
treatment
paradigm ?



Lifelong debilitating disease ---> possibility of development of comorbidities ---> more aggressive management in a subset of children?

What's wrong with Mia?

- ▶ This is Mia*, she is 12 years old and has been living with moderate to severe psoriasis for six years
- ▶ Mia's parents are concerned as she has been increasingly withdrawn
- ▶ With a CDLQI of 12, Mia's quality of life is being effected



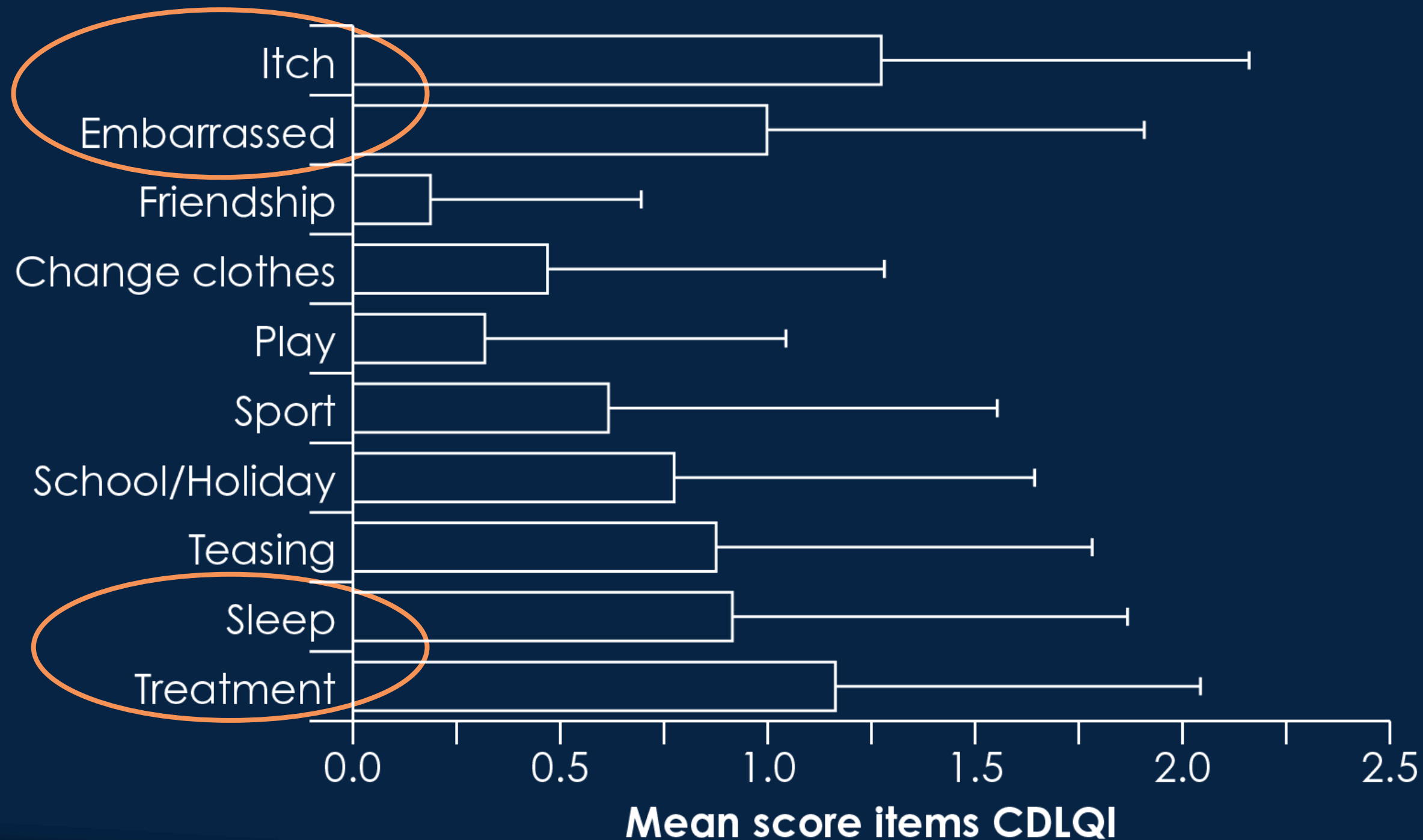
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the animation on
the Learning Zone



Paediatric psoriasis and quality of life

- ▶ Profound long-term impact on the psychological health of affected children¹
- ▶ interferes with self-esteem, family and social relationships²
- ▶ negatively influences the social-emotional development of children and adolescents²
- ▶ the age of first presentation may substantially affect an individuals' life course, with younger patients more susceptible to cumulative life course impairment³

CDLQI in juvenile psoriasis: results from the Child-CAPTURE patient registry



Effect of Age at Diagnosis on Chronic Quality of Life and Long-Term Outcomes of Individuals with Psoriasis

- ▶ Patients diagnosed at younger age (<16y):
 - ▶ More likely to have a greater lifetime DLQI
 - ▶ Have felt depressed
 - ▶ Believe that psoriasis had caused their depression
 - ▶ Experience life time sleep problems
 - ▶ Use recreational drugs
 - ▶ Hide their psoriasis over their lifetime
 - ▶ Experience more lifetime discrimination in social settings

Comorbidities - Psychiatric disorders

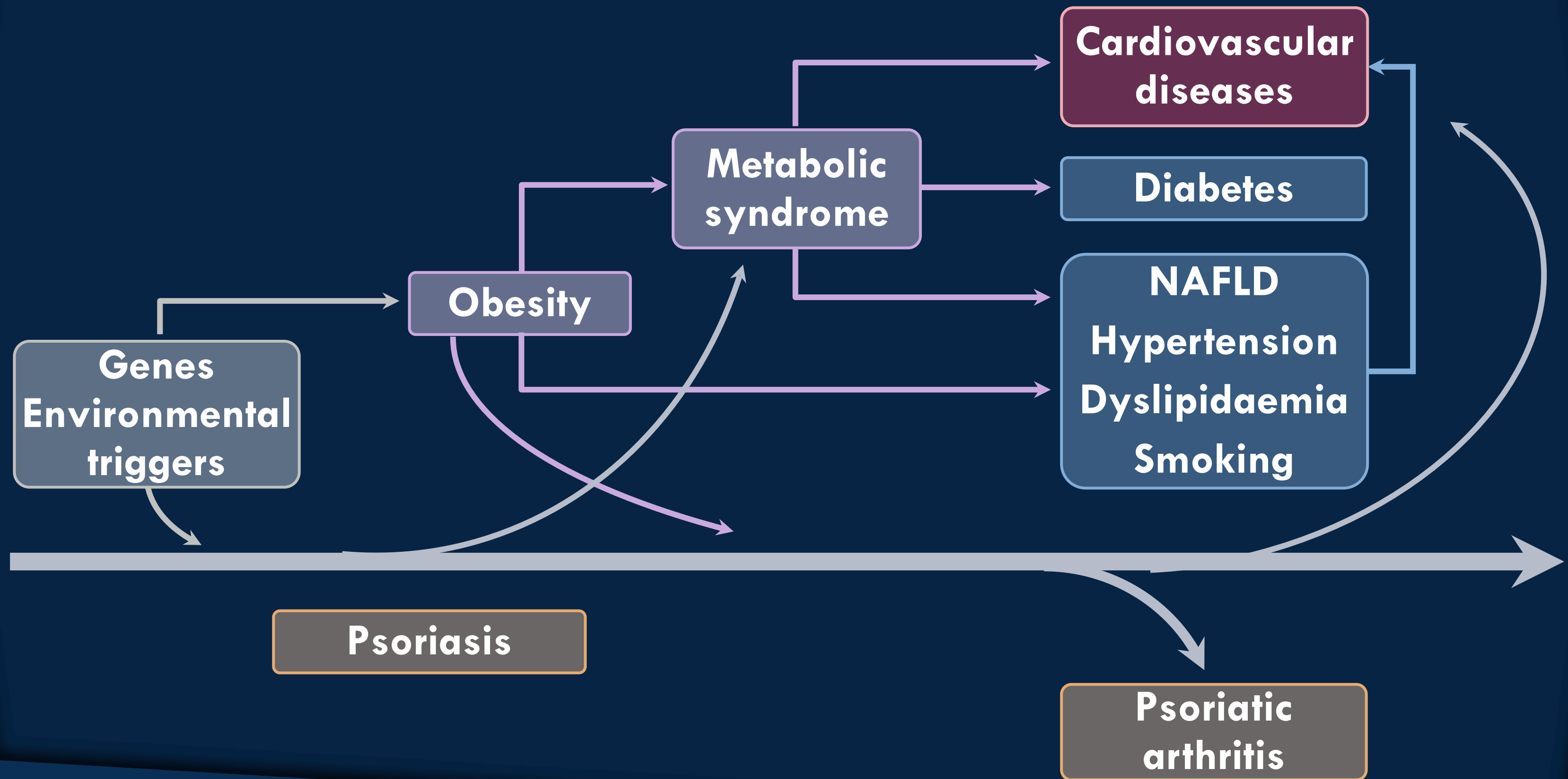
- ▶ Retrospective observational study of medical claims (n=7404):
 - increased risk, especially depression and anxiety¹
- ▶ Cross-sectional study (n=48):
 - higher depression score in child group (8-12 years)²
- ▶ Descriptive cross-sectional study (n=101 adults):
 - early onset psoriasis (< age 20) more anxious and depressed than late onset³

Other comorbidities in paediatric psoriasis

Prevalence of comorbidities (%) in persons in the age range 0–20 years with psoriasis (n = 2549) and without psoriasis (n = 331 758)

Diagnosis	% without psoriasis	% with psoriasis	Prevalence rate (95% confidence interval)
Crohn's disease	0.14	0.51	3.69 (2.15 – 6.35)
Hyperlipidaemia	0.99	2.12	2.15 (1.65 – 2.80)
Diabetes mellitus	0.43	0.86	2.01 (1.32 – 3.04)
Arterial hypertension	0.83	1.65	1.89 (1.47 – 2.67)
Rheumatoid arthritis	4.90	8.40	5.21 (1.40 – 19.44)
Obesity	4.90	8.40	1.70 (1.49 – 1.93)
Ischaemic heart disease	0.49	0.75	1.52 (0.97 – 2.38)
Ulcerative colitis	0.10	0.12	1.13 (0.38 – 3.33)
All comorbidities (at least one)	7.20	14.40	2.00 (1.82 – 2.20)

Does undertreatment facilitate the 'psoriatic march'?



Early intervention? (I)

REVIEW ARTICLE

BJD
British Journal of Dermatology

Management of psoriasis as a systemic disease: what is the evidence?

N.J. Korman^{1,2}

Evidence in **adults** demonstrates that biological treatment may prevent inflammatory damage associated with psoriasis comorbidities¹

- ▶ RS: patients on TNF inhibitors significantly lower risks for myocardial infarction compared with patients receiving topicals and MTX²
- ▶ 2 RS: TNF inhibitor cohort had lower risks for major cardiovascular events when compared with the phototherapy cohort³
- ▶ Prospective study (220 pts): improvement in PASI score associated with reduced aortic inflammation⁴

1.Korman. Br J Dermatol 2020 2. Wu et al. Arch derm 2012; J Am Acad 2017 3. Wu et al. J Am Acad 2018; J Eur Acad Dermatol Venereol 2018 4. Dey et al. JAMA Cardiol 2017

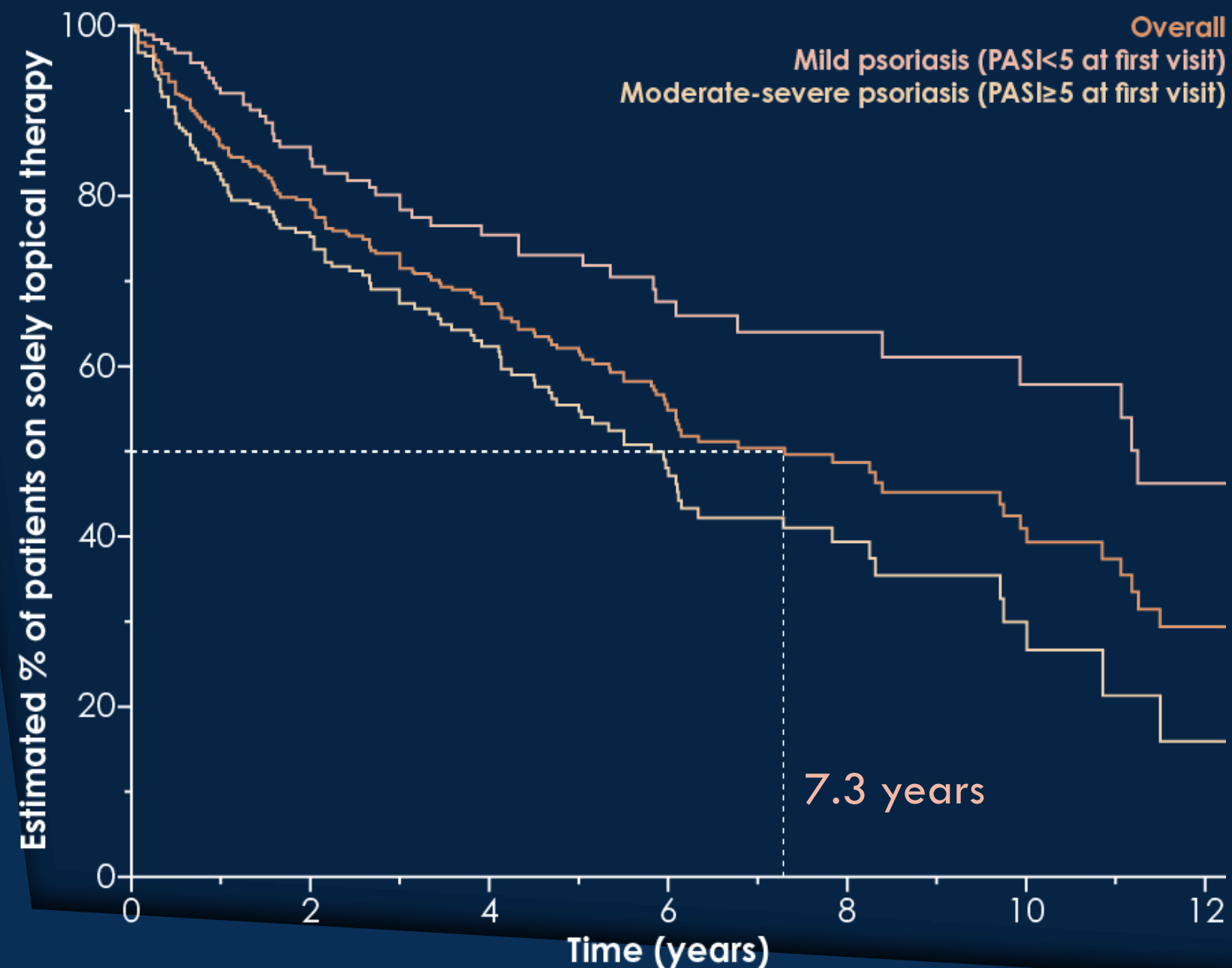
RS, retrospective cohort study

Early intervention? (II)

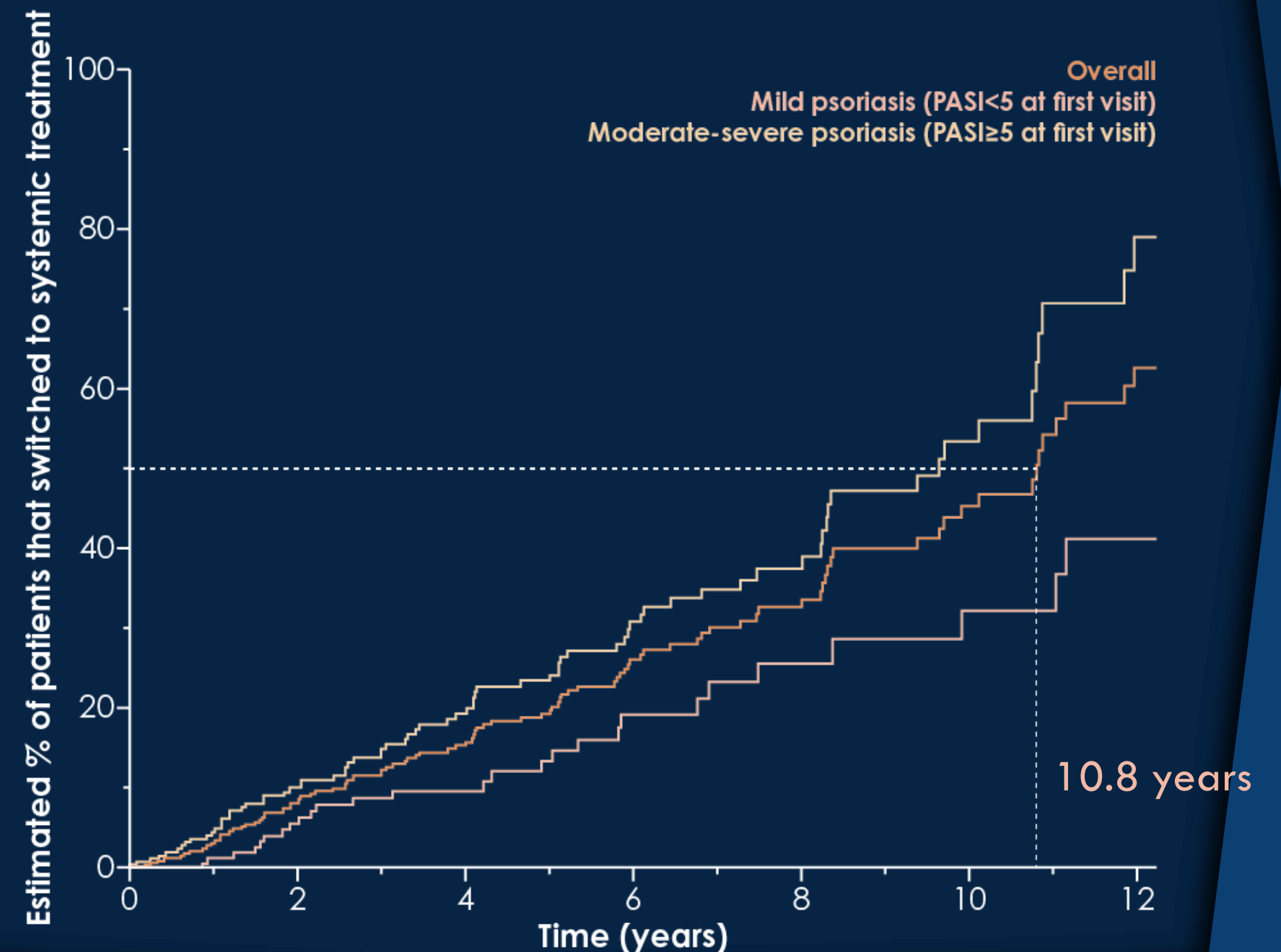
- ▶ RS: no significant differences in overall MI risk between patients treated with conventional systemics and biologics compared to treatment with UVB¹
- ▶ RS: similar risk for cardiovascular events with biologics compared to MTX²
- ▶ Prospective Vascular Inflammation in Psoriasis (VIP) trials are evaluating the effects of ustekinumab, secukinumab and apremilast on aortic inflammation and on levels of biomarkers associated with metabolic and cardiovascular risks³
 - ▶ important insights into the role that biological agents play in treating systemic inflammation associated with psoriasis

ChildCAPTURE: treatment persistence in 448 paediatric psoriasis patients

Median time from psoriasis onset until solely topical therapy discontinuation



Median time from psoriasis onset until switch to first systemic treatment



Summary

- ▶ Paediatric psoriasis negatively influences quality of life, self-esteem and social emotional development
- ▶ This could ultimately lead to life course impairment
- ▶ Paediatric psoriasis is associated with comorbidities
- ▶ Undertreatment might facilitate the psoriatic march
- ▶ Future studies: insights into the role that biological agents play in treating systemic inflammation associated with psoriasis
 - ▶ Assist the discussion about early aggressive intervention in paediatric psoriasis



What is playing safe in paediatric psoriasis?

Tiago Torres

Professor of Dermatology, Instituto de Ciências
Biomédicas Abel Salazar at the University of
Porto

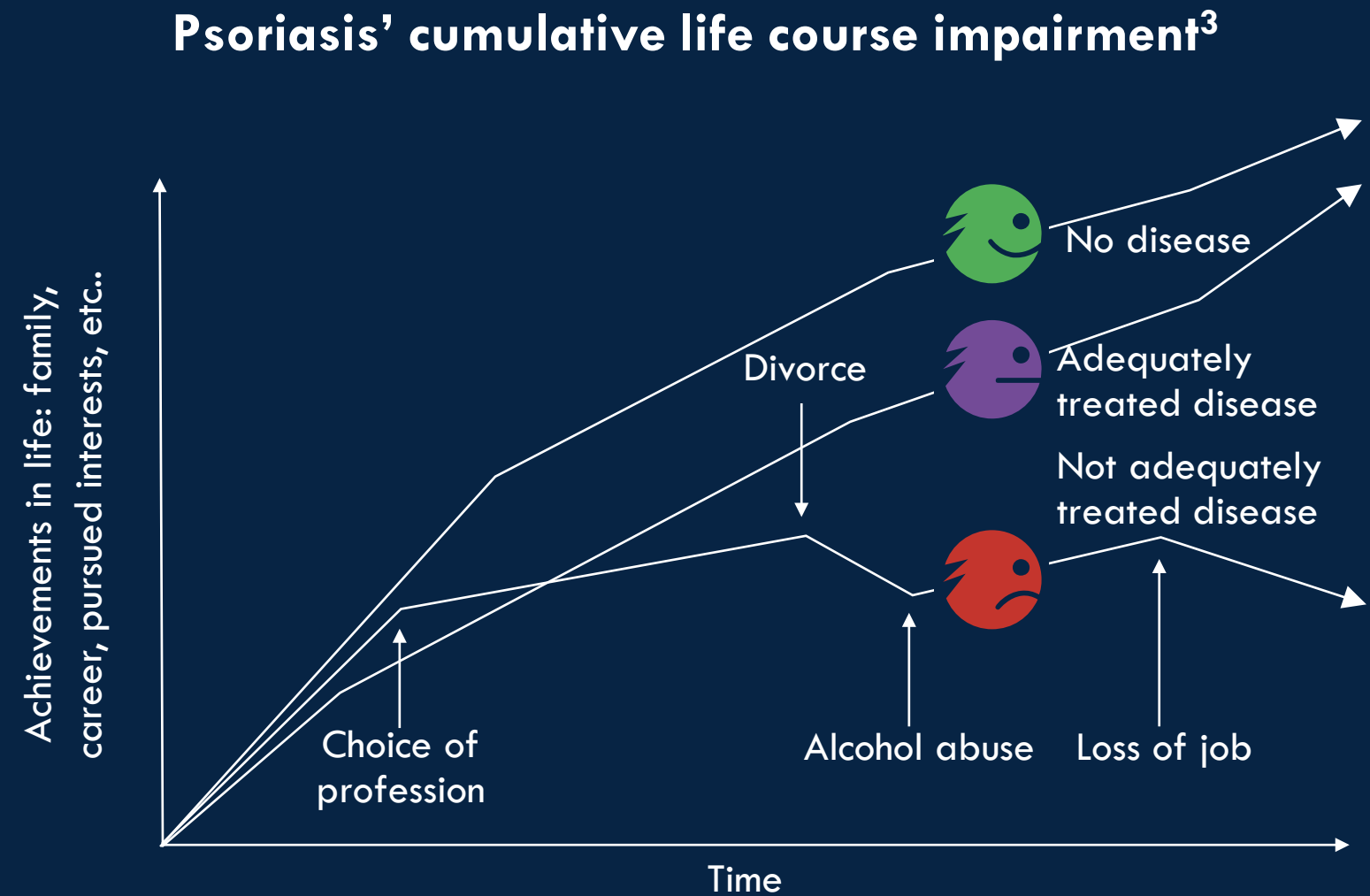
Unit for Multidisciplinary Research in
Biomedicine - University of Porto, Portugal

Disclosures

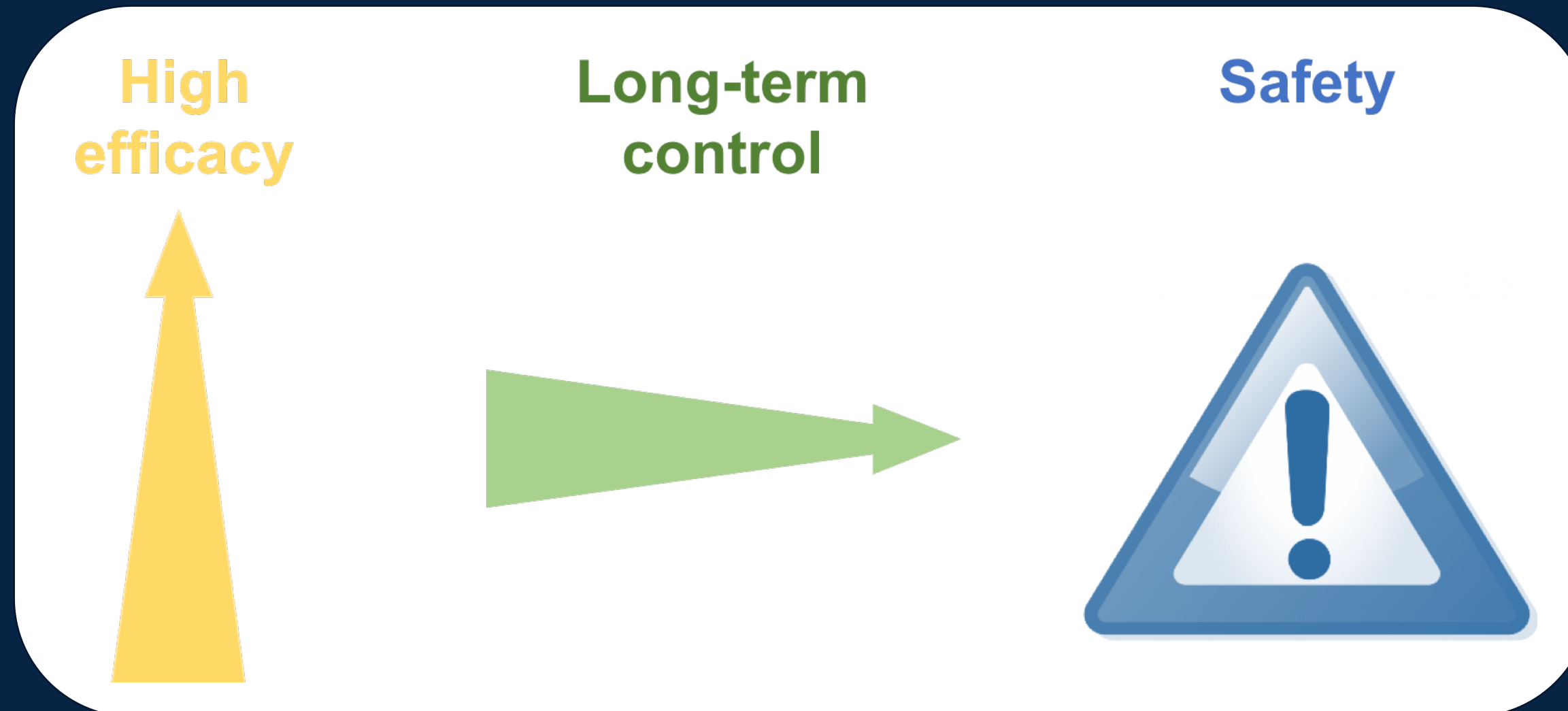
AbbVie, Almirall, Amgen, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, BMS, Celgene, Eli Lilly, Janssen, LEO Pharma, MSD, Novartis, Pfizer, Sandoz, and Samsung-Bioepis

Long-term impact of paediatric psoriasis

- ▶ Early and appropriate treatment of psoriasis critical in the paediatric population
 - ▶ Paediatric psoriasis associated with several medical comorbidities¹
 - ▶ Children with psoriasis likely to experience:
 - ▶ Social discrimination and stigmatisation^{1,2}
 - ▶ Impairment in emotional, social and school functioning^{1,2}
- ▶ Impact of psoriasis may have implications in children's future and personality resulting in an inability to achieve 'full-life potential' (cumulative life course impairment)³

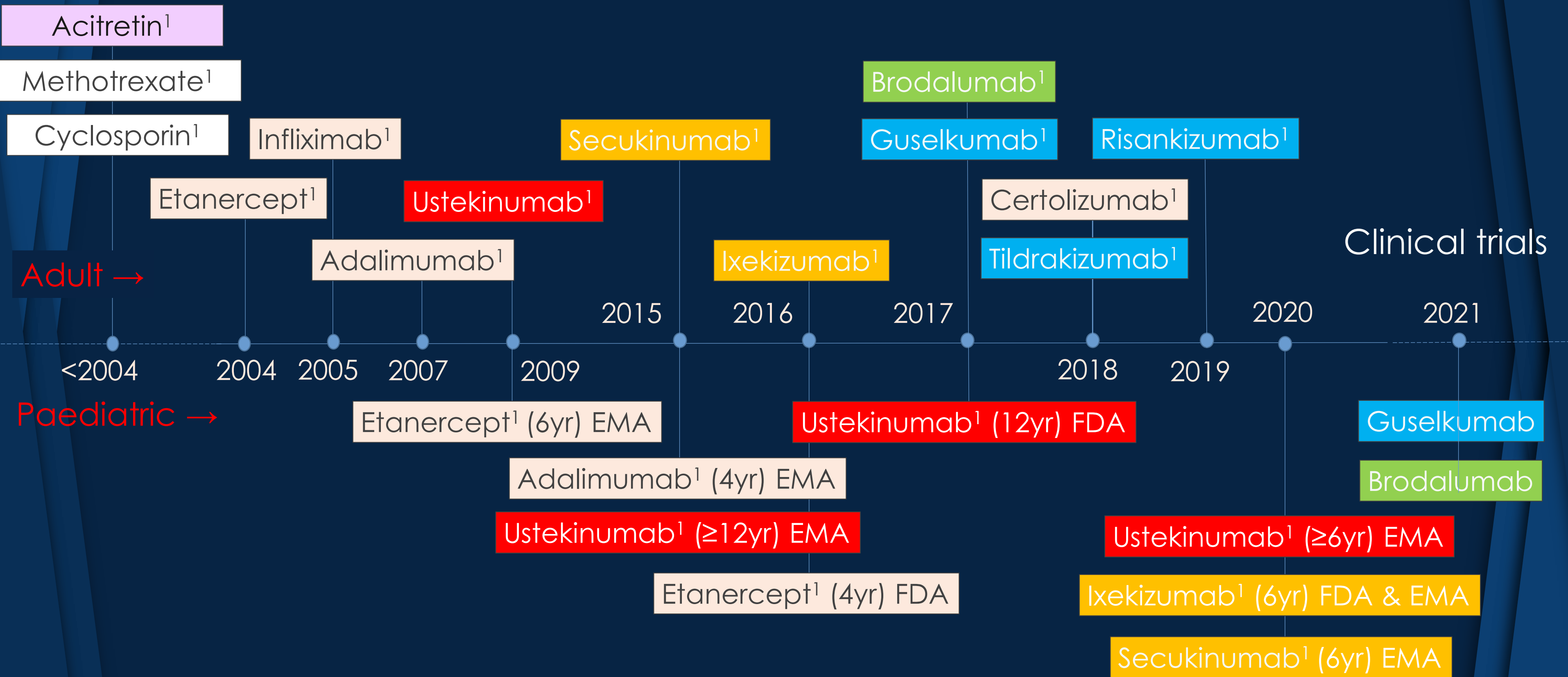


Goals in the management of paediatric psoriasis



The main goal in the management of psoriasis (particularly in children) must be to clear or almost clear the disease, long-term control, the least toxicity and as few side effects as possible

Evolving treatment landscape in adult and paediatric psoriasis



1. FDA-Approved Drugs. Available at: <https://www.accessdata.fda.gov/scripts/cder/daf/> (accessed September 2020); 2. ClinicalTrials.gov. Available at: <https://clinicaltrials.gov/ct2/show/NCT04036435> (accessed September 2020); 3. ClinicalTrials.gov. Available at: <https://clinicaltrials.gov/ct2/show/NCT03535194> (accessed September 2020); 4. ClinicalTrials.gov. Available at: <https://www.clinicaltrials.gov/ct2/show/NCT03536884> (accessed September 2020); 4. Menter A, et al. J Am Acad Dermatol. 2020;82(1):161-201.

Systemic therapies used for paediatric psoriasis

Conventional systemic therapy	EMA	FDA	Evidence
Methotrexate	Not approved		Evidence in adult population Other paediatric diseases Prospective/retrospective cohort studies Used extensively by dermatologists in clinical practice
Cyclosporine	Not approved		Evidence in adult population Other paediatric diseases Anecdotal evidence in paediatric psoriasis
Acitretin	Not approved		Evidence in adult population Anecdotal evidence in paediatric psoriasis

Biologic therapy	EMA	FDA	Evidence
Etanercept	≥6 years (2009)	≥4 years (2016)	RCT Long-term evaluation (open label) RWE studies
Adalimumab	≥4 years (2015)	-	RCT Long-term evaluation (open label) REW studies
Ustekinumab	≥12 years (2015)	≥12 years (2017)	RCT Long-term evaluation (open label) REW studies
Ixekizumab	≥6 years (2020)	≥6 years (2020)	RCT
Secukinumab	≥6 years (2020)	-	RCT

Current management of paediatric psoriasis:

Conventional systemic therapy

- ▶ Conventional systemic therapy are off-label for the indication of paediatric psoriasis
 - ▶ Although can offer effective control, use may be limited by contraindications, AEs and toxicities and require regular monitoring and generally not recommended for long-term use
- ▶ Most paediatric patients with moderate to severe plaque psoriasis still initially treated with conventional systemic therapies
 - ▶ MTX most frequent (69.2%), followed by biologics (primarily etanercept) (27.2%), acitretin (14.6%) and cyclosporine (7.7%)¹
- ▶ Inadequate response and intolerance to conventional systemic therapy not uncommon^{2,3}
- ▶ Up to 80% of paediatric patients on conventional systemic non-biologic therapies discontinue treatment in the first 2 years
 - ▶ Main reasons include lack of efficacy and AEs

Drug	Mechanism	Dosing regimens	Contraindications	Side effects	Comments
Cyclosporine	Inhibits T lymphocytes and production of interleukin-2 and interferon- γ	1.5-5 mg/kg per day (max dose = 4 mg/kg per day in US, 5 mg/kg per day internationally; use limited to 1-2 years depending on country)	Active, serious infections; abnormal kidney function; uncontrollable hypertension; cancer or history of cancer (other than certain skin cancers); phototherapy	Decreased renal function, hypertension, hyperkalaemia, hypermagnesaemia, gingival hyperplasia, hypertrichosis, nausea, emesis, diarrhoea, arthralgia, headache, paraesthesia	Risk of cutaneous malignancy and lymphoma minimal in immunocompetent patients; many drug-drug reactions with cyclosporine; improvement can occur within 4-8 wks; taper doses after 1 to 3 mos of stable response
Methotrexate	Inhibits dihydrofolate reductase	In children, 0.1-0.4 mg/kg per wk (max 25 mg/wk); consider test dose up to 5 mg followed by lab monitoring after 1 wk to assess marrow toxicity; if no toxicity, increase dose incrementally to therapeutic effect	Alcoholism, liver disease, immunodeficiency syndromes, pregnancy or planning pregnancy, significant kidney or liver abnormalities, serious active infections, hematologic disorders	Nausea, vomiting, headache, diarrhoea, hepatotoxicity, interstitial pneumonitis, bone marrow suppression, photosensitivity, infections	Folic acid supplementation 6 or 7 d/wk may reduce gastrointestinal toxicity, tolerance
Acitretin	Oral retinoid; regulates epidermal cell growth and apoptosis	Initiate treatment at ≤ 0.5 -1 mg/kg per day to minimise toxicity	Severe liver or kidney disease, uncontrolled hyperlipidaemia, concurrent use of tetracycline or vitamin A derivatives; pregnancy	Mucocutaneous effects (xerosis, cheilitis, xerophthalmia; granulation tissue of nails); dyslipidaemia, high liver enzymes, rare skeletal hyperostosis, calcification of ligaments	Teratogen; avoid in women of child-bearing potential; response may be seen in as little as 3 wks, particularly effective for pustular psoriasis

AE, adverse events; MTX, methotrexate

1. Bronckers I, et al. JAMA Dermatol 2017; 153(11):1147-1157; 2. Van Geel MJ, et al. J Dermatolog Treat 2015;26:406-12; 3. Ergun T, et al. J Dermatol 2017;44:630-4

Adapted from: Marqueling AL, et al. Dermatol Clin. 2013;31:267-288; Eichenfield LF, et al. Pediatr Dermatol. 2018;00:1-12.

Current management of paediatric psoriasis:

Biologic therapy

- ▶ Safety data available for biologic therapy in the paediatric population
- ▶ Since 2009, 5 biologic agents evaluated in RCTs and approved for the treatment of paediatric psoriasis (≥ 4 years or ≥ 6 years)¹⁻⁶
- ▶ Long-term safety data available for etanercept and adalimumab^{7,8}
- ▶ Real-world data⁹⁻¹¹

No new safety signals observed and safety profile consistent with that observed in long-term studies in adults with psoriasis and children with other diseases¹⁻⁶

Biologic therapy	EMA	FDA
Etanercept	≥ 6 years (2009)	≥ 4 years (2016)
Adalimumab	≥ 4 years (2015)	-
Ustekinumab	≥ 12 years (2015)	≥ 12 years (2017)
	≥ 6 years (2020)	≥ 6 years (2020)
Ixekizumab	≥ 6 years (2020)	≥ 6 years (2020)
Secukinumab	≥ 6 years (2020)	-

RCT, randomised controlled trials.

1. Langley RG, et al. J Am Acad Dermatol. 2011;64(1):64-70; 2. Papp K, et al. Lancet. 2017 Jul 1;390(10089):40-49; 3. Landells I, et al. J Am Acad Dermatol. 2015;73(4):594-603; 4. Philipp S, et al. Br J Dermatol. 2020;Mar 16 (online ahead of print); 5. Paller AS, et al. Br J Dermatol. 2020;183(2):231-241; 6. Magnolo N, et al. Presented at AAD VMX 2020; 7. Paller AS, et al. J Am Acad Dermatol. 2010;63(5):762-768; 8. Thaçi D, et al. Br J Dermatol. 2019;181(6):1177-1189; 9. Di Lernia V, et al. Dermatol Ther. 2019 Nov;32(6):e13091; 10. Phan C, et al. J Eur Acad Dermatol Venereol. 2019;33(10):1984-1992; 11. Klufas DM, et al. Pediatr Dermatol. 2016;33(2):142-149.

Safety of biologics in paediatric psoriasis (1)

Etanercept¹⁻⁵

Adalimumab^{4,6-8}

Ustekinumab^{9,10}

Study design	48-week randomised, double-blind, Phase 3 trial 211 paediatric patients (≥ 4 to < 18 years) - OLE up to 264 weeks - Long-term safety in 1182 patients to Weeks 96 and 264	52-week, randomised, Phase 3 trial 114 paediatric patients (≥ 4 to < 18 years) 16-week period vs MTX and 52-week LTE	52-week, double-blind, placebo-controlled Phase 3 trial 110 paediatric patients (≥ 12 to 17 years) - AEs monitored through Week 609 52-week, open-label, single-arm, Phase 3 44 pts (≥ 6 to < 12 years) - Safety evaluated through Week 56
Safety results	8 patients reported serious AEs by Week 26 1 thought to be treatment related (cellulitis) - No cases of opportunistic infection or malignancy reported up to 264 weeks - Most commonly reported AEs: URTIs (37.6%), nasopharyngitis (26.0%), headache (21.5%)	- Safety profile during 52-week LTE similar to 16-week IT period profile - Low numbers of serious adverse events, no serious infections - The most common adverse events were nasopharyngitis and URTIs - Safety profile consistent with the known in adults with psoriasis	No new safety concerns Most commonly reported being nasopharyngitis, pharyngitis, and upper respiratory infection. injection site reaction No deaths, malignancies, major adverse cardiovascular, cases of tuberculosis or opportunistic infection
RWE	Similar results (up to 2 years)		

AE, adverse event; IT, initial treatment; LTE, long-term extension; MTX, methotrexate; RWE, real world evidence; URTI, upper respiratory tract infection;

1. Paller AS, et al. N Engl J Med. 2008;358(3):241–251; 2. Paller AS, et al. J Am Acad Dermatol. 2010;63(5):762–768.; 3. Paller AS, et al. J Am Acad Dermatol. 2016;74(2):280–287.e1; 4. Klufas DM, et al.

Pediatr Dermatol. 2016;33(2):142–149; 5. Phan C, et al. J Eur Acad Dermatol Venereol. 2019 Oct;33(10):1984–199; 6. Papp K, et al. Lancet. 2017;390:40–49; 7. Thaçi D, et al. Br J Dermatol. 2019;181(6):1177–1189;

8. Di Lernia V, et al. Expert Opin Biol Ther. 2017; 17: 1553–1556; 9. Landells I, et al. J Am Acad Dermatol. 2015;73(4):594–603; 10. Philipp S, et al. Br J Dermatol. 2020.

Safety of biologics in paediatric psoriasis (2)

	Ixekizumab ¹	Secukinumab ^{2,3}
Study design	• 48-week, randomised, double-blind, placebo-controlled Phase 3 study ▪ 115 ixekizumab patients vs 56 placebo patients, ≥6 to <18 years through Week 12, followed by OLE to Week 48	• Two 52-week Phase 3 trials in children and adolescents aged 6 to <18 years: ▪ Open-label, two-arm, parallel-group, multicentre study in children with moderate-to-severe plaque psoriasis (N=85) ▪ Randomised, double-blind, placebo and etanercept-controlled study (N=16)
Safety results	• Safety profile generally consistent with that observed in adults ▪ Most AEs mild to moderate in severity ▪ No serious infections reported	• Safety profile comparable and consistent with established adult psoriasis indication • No new safety signals were observed in children up to 52 weeks • Infections, nasopharyngitis and mild neutropenia most common AEs

AE, adverse event; OLE, open label extension

1. Paller AS, et al. Br J Dermatol. 2020;183(2):231-241; 2. Magnolo N, et al. Presented at AAD VMX 2020; 3. Novartis Press Release 2020. Available at: <https://www.novartis.com/news/media-releases/novartis-cosentyx-receives-eu-approval-first-line-systemic-treatment-pediatric-psoriasis> (accessed September 2020)

Biologic therapies in development for paediatric psoriasis (Phase 2 and 3 clinical trials)

Biologic therapy	Clinical trial		Status	
Brodalumab	NCT04305327	Efficacy and safety of brodalumab in adolescents from 12 to 17 years of age with moderate-to-severe plaque psoriasis	Phase 3	Not yet recruiting
Guselkumab	NCT03451851	A study to evaluate the efficacy, safety, and pharmacokinetics of subcutaneously administered guselkumab for the treatment of chronic plaque psoriasis in paediatric participants	Phase 3	Recruiting
Risankizumab	NCT04435600	A study of subcutaneous risankizumab injection for paediatric participants with moderate to severe plaque psoriasis to assess change in disease symptoms	Phase 3	Recruiting
Tildrakizumab	NCT03997786	A study of tildrakizumab in paediatric subjects with chronic plaque psoriasis	Phase 3	Recruiting
Non-biologic therapy				
Apremilast	NCT02576678	A study of safety, tolerability and pharmacokinetics of apremilast (CC-10004) in paediatric subjects with moderate to severe plaque psoriasis	Phase 2	Completed

Should we consider biologics as first-line therapy for paediatric psoriasis?

- ▶ Biologic therapy vs conventional systemic therapy
 - ▶ Robust evidence (RTC, long-term efficacy and safety data and RWE)
 - ▶ On-label therapy
 - ▶ Higher efficacy
 - ▶ Fewer treatment-related toxic effect
 - ▶ Less monitoring
- ▶ Recommendations/guidelines proposing biologics should be considered as first-line treatment for children with severe plaque psoriasis^{1,2,3}

ORIGINAL ARTICLE

Treatment of severe psoriasis in children: recommendations of an Italian expert group

Anna Belloni Fortina¹ • Federico Bardazzi² • Samantha Berti³ • Claudia Carnevale⁴ • Vito Di Lernia⁵ • Maya El Hachem⁴ • Iria Neri² • Carlo Mario Gelmetti⁶ • Viviana Lora⁷ • Carlo Mazzatenta⁸ • Mirella Milioto⁹ • Gaia Moretta¹⁰ • Annalisa Patrizi² • Ketty Peris¹⁰ • Alberto Villani¹¹

Management of Pediatric Plaque Psoriasis using Biologics

Perla Lansang, MD, James N. Bergman, MD, Loretta Fiorillo, MD, Marissa Joseph, MD, Irene Lara-Corrales, MSc, MD, Danielle Marcoux, MD, Catherine McCuaig, MD, Elena Pope, MSc, MD, Vimal H. Prajapati, MD, Sue ZJ. Li, PhD, Ian Landells, MD



Guideline

DOI: 10.1111/ddg.13936

S2k guidelines for the treatment of psoriasis in children and adolescents – Short version part 2

Lisa Eisert¹, Matthias Augustin², Sabine Bach³, Martin Dittmann¹, Renate Eiler³, Regina Fölster-Holst⁴, Sascha Gerdes⁴, Henning Hamm⁵, Peter Höger⁶, Gerd Horneff⁷, Ralph von Kiedrowski⁸, Sandra Philipp⁹, Marc Pleimes¹⁰, Martin Schlaeager¹¹, Volker Schuster¹², Petra Staubach¹³, Tobias Weberschock^{14,15}, Ricardo Niklas Werner¹, Alexander Nast^{1*}, Michael Sticherling^{16*}

Take home messages

- ▶ Psoriasis may have implication in children's future and personality, resulting in an inability to achieve 'full-life potential'
- ▶ Early, effective, and safe treatment of psoriasis is critical in the paediatric population
- ▶ Conventional systemic therapies are off-label for paediatric psoriasis
 - ▶ Use may be limited by contraindications, AEs and toxicities
 - ▶ Generally not recommended for long-term use and require regular monitoring
- ▶ Biologic agents have shown to be safe in short and long-term RCTs
 - ▶ No new safety signals
 - ▶ Safety profile consistent with that observed in adults with psoriasis and children with other diseases
- ▶ Several biologic agents already approved while other are in Phase 3 studies

Given the potential need for life-long treatment and based on current efficacy and safety evidence, biologic therapy should be considered first-line therapy in the treatment of moderate-to-severe paediatric psoriasis

Final thoughts

- ▶ Based on current efficacy and safety evidence, biologic therapy should be considered first-line therapy in the treatment of moderate-to-severe paediatric psoriasis
- ▶ But, is efficacy sufficiently greater to warrant a switch to newer biologics?
- ▶ IS PASI 75 enough?

EADV Virtual Symposium

Friday 30th October 13:00-14:00 CET

Paediatric psoriasis Full clearance can be up to you

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Welcome and introductions



Please use the chat function to submit questions to the faculty. Questions will be addressed during the Q&A discussion



The recording will be available to watch after the virtual symposium

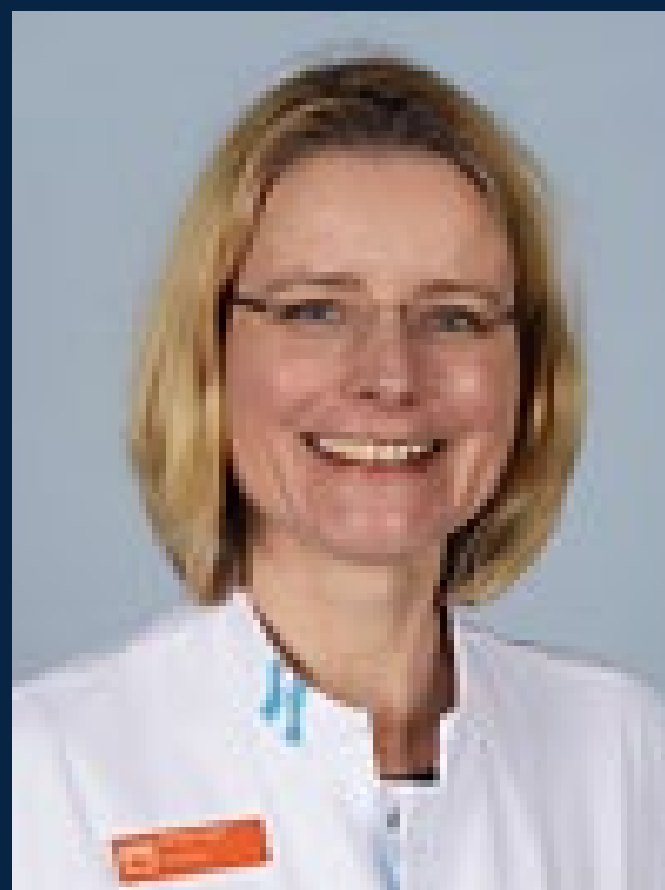
Our faculty

Professor Amy Paller



Professor and Chair of Dermatology and Professor of Paediatrics at Northwestern University's Feinberg School of Medicine, Chicago, USA

Professor Marieke Seyger



Associate Professor of Dermatology in the Department of Dermatology, Radboud University Nijmegen Medical Centre, The Netherlands

Professor Tiago Torres



Professor of Dermatology at the Instituto de Ciências Biomédicas Abel Salazar at the University of Porto, Portugal

Our agenda

Duration	Title	Speaker
3 min.	Welcome & introduction	Professor Amy Paller (Chair)
15 min.	The dangers of undertreatment in paediatric psoriasis	Professor Marieke Seyger
15 min.	What is playing safe in paediatric psoriasis?	Professor Tiago Torres
15 min.	PASI 75 is not enough	Professor Amy Paller
10 min.	Panel discussion and live Q&A	All

An illustration of a person's face, primarily in shades of orange and red, set against a dark blue background. Three blue silhouettes of construction workers are shown painting the face. One worker is on a scissor lift on the left, painting the forehead. Another worker is on a rope ladder on the right, painting the cheek. A third worker is at the bottom, painting the chin. The face has closed eyes and a serene expression.

PASI 75 is not enough

Professor Amy Paller

Professor and Chair of Dermatology and Professor of
Paediatrics at Northwestern University's Feinberg School of
Medicine, Chicago, USA

Disclosures

Professor Paller has received funding from AbbVie, AnaptysBio, BMS, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Regeneron Pharmaceuticals, Inc. – investigator; Almirall, Amgen, Asana, BMS, Boehringer Ingelheim, Castle Creek, Dermavant, Dermira, Eli Lilly, Exicure, Forte, Galderma, Lenus, LEO Pharma, Meda, Meiji Seika, Novan, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, Sol Gel – consultant.

What is the PASI score?

- ▶ The PASI score is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance:¹

- ▶ Erythema
- ▶ Induration
- ▶ Desquamation

- ▶ PASI is used for monitoring response to treatments in clinical trials and as a research tool to judge the severity of psoriasis¹
- ▶ It is rarely used by dermatologists in clinical practice to guide management¹

The PASI severity score²

Intensity	Absent	Mild	Moderate	Severe	Very severe
<u>Erythema</u> (redness)	 Score 0	 Score 1	 Score 2	 Score 3	 Score 4
<u>Induration</u> (thickness)	 Score 0	 Score 1	 Score 2	 Score 3	 Score 4
<u>Desquamation</u> (scaling)	 Score 0	 Score 1	 Score 2	 Score 3	 Score 4

PASI 75, PASI 90, and PASI 100

Defining PASI 75, 90 and 100¹

PASI 75	PASI 90	PASI 100
≥75% improvement in the PASI	≥90% improvement in the PASI	≥100% improvement in the PASI

- ▶ Historically, PASI 75 was considered an appropriate response to biologic therapy²
- ▶ However, the emergence of new therapeutic classes has brought into focus the need to "*set the bar higher*" and adopt PASI 90 as the new standard for a good response³

PASI 90 response: A new standard in therapeutic efficacy for psoriasis

- ▶ Although PASI 75 meets therapeutic expectations in most patients, PASI 90 has a significantly higher impact on QoL improvement¹
- ▶ PASI 90 is considered as treatment success by the EMA²
- ▶ Introduction of anti-IL17 and anti-IL23 targeted treatments in clinical practice bears the promise of achieving $\geq$ PASI 90 response in the majority of patients³

Quality of life in paediatric dermatology patients: CDLQI

- ▶ Skin diseases, including psoriasis, can severely impact QoL in children¹⁻⁴
- ▶ The CDLQI is the most widely used instrument for measuring impact of skin disease on QoL in children^{3,4}

- ▶ CDLQI involves 10 questions about impact of skin disease on the life of the affected child over the previous week^{3,4}
 - ▶ Topics covered include symptoms, embarrassment, friendships, clothes, playing, sports, school, bullying, sleep and impact of treatment
 - ▶ Scoring for each question is “Very much”[3] to “Not at all”[0]
 - ▶ Severity bands for overall CDLQI scores
 - ▶ 0–1 = no effect
 - ▶ 2–6 = small effect
 - ▶ 7–12 moderate effect
 - ▶ 13–18 = very large effect
 - ▶ 19–30 = extremely large effect.

The image shows a sample of the CDLQI questionnaire titled "Trouble Skin". It includes instructions and six numbered questions with corresponding illustrations of a dog and a rating scale from 0 to 3.

Trouble Skin

The aim of the questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please ✓ one box for each question.

1 How itchy, 'scratchy', sore or painful has your skin been?

2 How upset or embarrassed, self-conscious or sad have you been because of your skin?

3 How much has your skin affected your friendships?

4 How much have you changed or worn different or special clothes/shoes because of your skin?

5 How much has your skin trouble affected going out, playing or doing hobbies?

6 How much have you avoided swimming or other sports because of your skin trouble?

Very much
Quite a lot
A little
Not at all

Children's Dermatology Life Quality Index

CDLQI, Children's Dermatology Life Quality Index; QoL, quality of life.

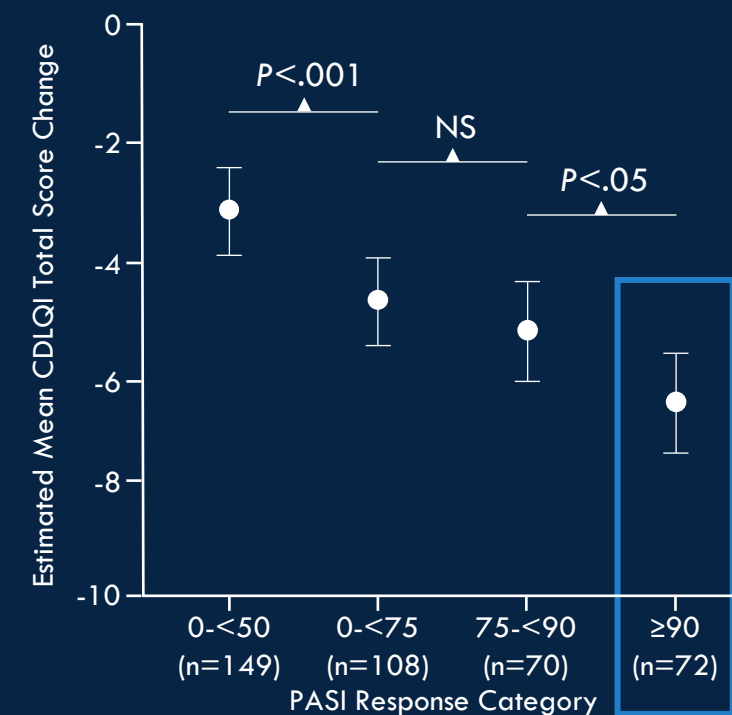
1. Menter A, et al. J Am Acad Dermatol. 2020;82(1):161-201; 2. Bruins FM, et al. JAMA Dermatol. 2020;156(1):72-76; 3. Lewis-Jones MA. Finlay AY. Br J Dermatol. 1995;132(6):942-9; 4. Olsen JR, et al. Br J Dermatol. 2016;174(4):853-61. © M. S. Lewis-Jones, A. Y. Finlay. June 1993. Illustrations ©Media Resources Centre, UWCM. Dec 1996

Why is PASI 75 not enough when treating children with moderate to severe psoriasis?

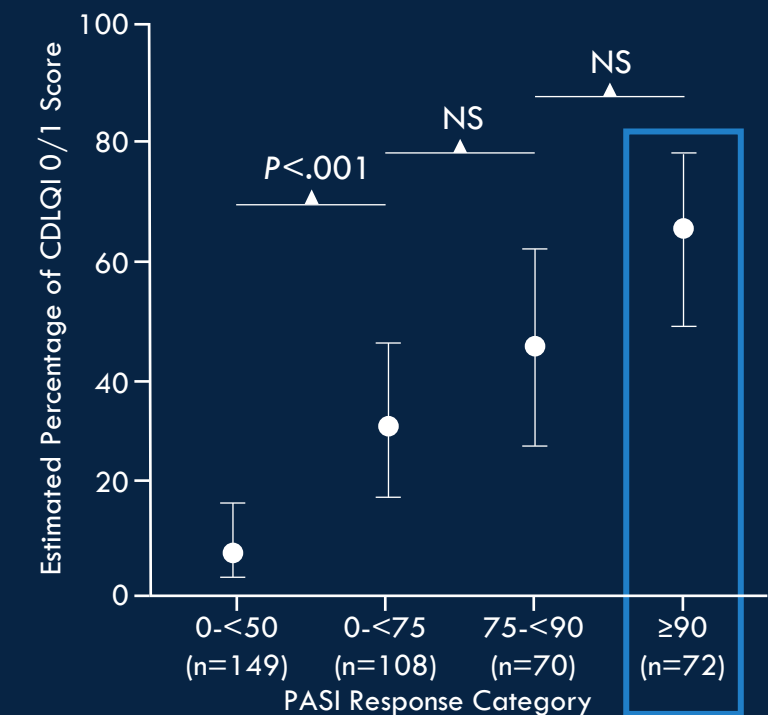
- ▶ Paediatric psoriasis is associated with reduced QoL, which is directly related to disease severity^{1,2}
- ▶ Treatment of psoriasis leading to skin clearance is associated with improved QoL, especially in paediatric patients²
- ▶ Greatest improvements in QoL are associated with:
 - ▶ PASI 90 or greater
 - ▶ $\geq 90\%$ decrease in BSA involvement
 - ▶ Systemic treatments

Improvements in QoL by PASI²

A. CDLQI changes by PASI response categories



C. CDLQI achievement by PASI response categories



What's wrong with Mia?

- ▶ Let's meet Mia*. She has a PASI score of 12 and a CDLQI of 12, showing the effect of her psoriasis on her QoL
- ▶ Mia has tried multiple topical and systemic treatments but, while well tolerated, these therapies only achieved mild responses and have led to subsequent relapses and frequent flare-ups



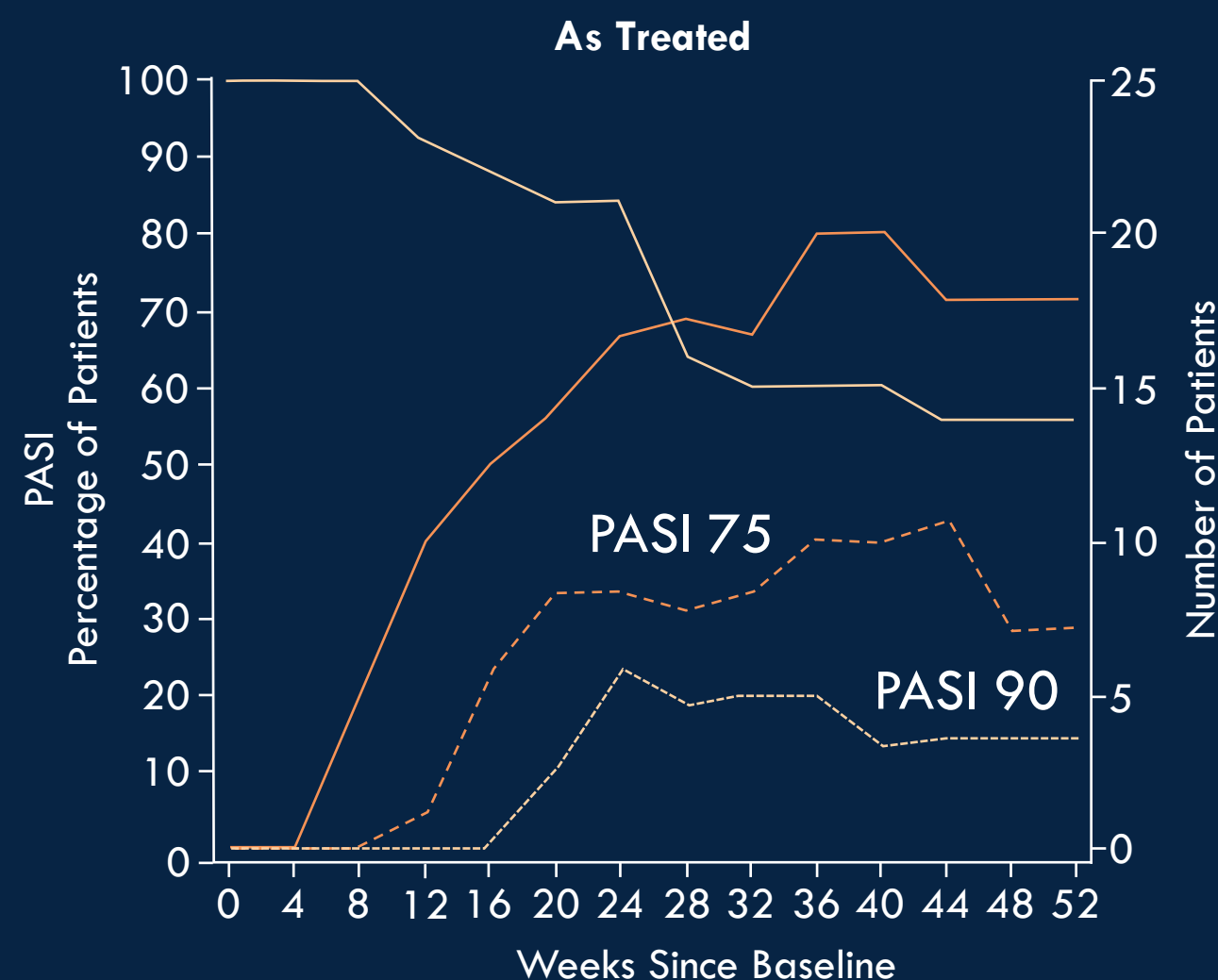
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Methotrexate: Most commonly used systemic treatment for paediatric psoriasis – available for decades

- ▶ MTX, approved in 1972, has been used for more than 4 decades in the treatment of psoriasis¹
- ▶ Efficacy on the PASI score and QoL²
 - ▶ Only 40% of children achieve PASI 75 at 48 weeks²
 - ▶ Decrease in CDLQI 9.0 to 3.8 at 24 weeks²
- ▶ Slow to act²
- ▶ Associated with toxicities²

Percentage of improvement compared with baseline of the PASI and BSA, using the as treated analysis and LOCF, respectively²



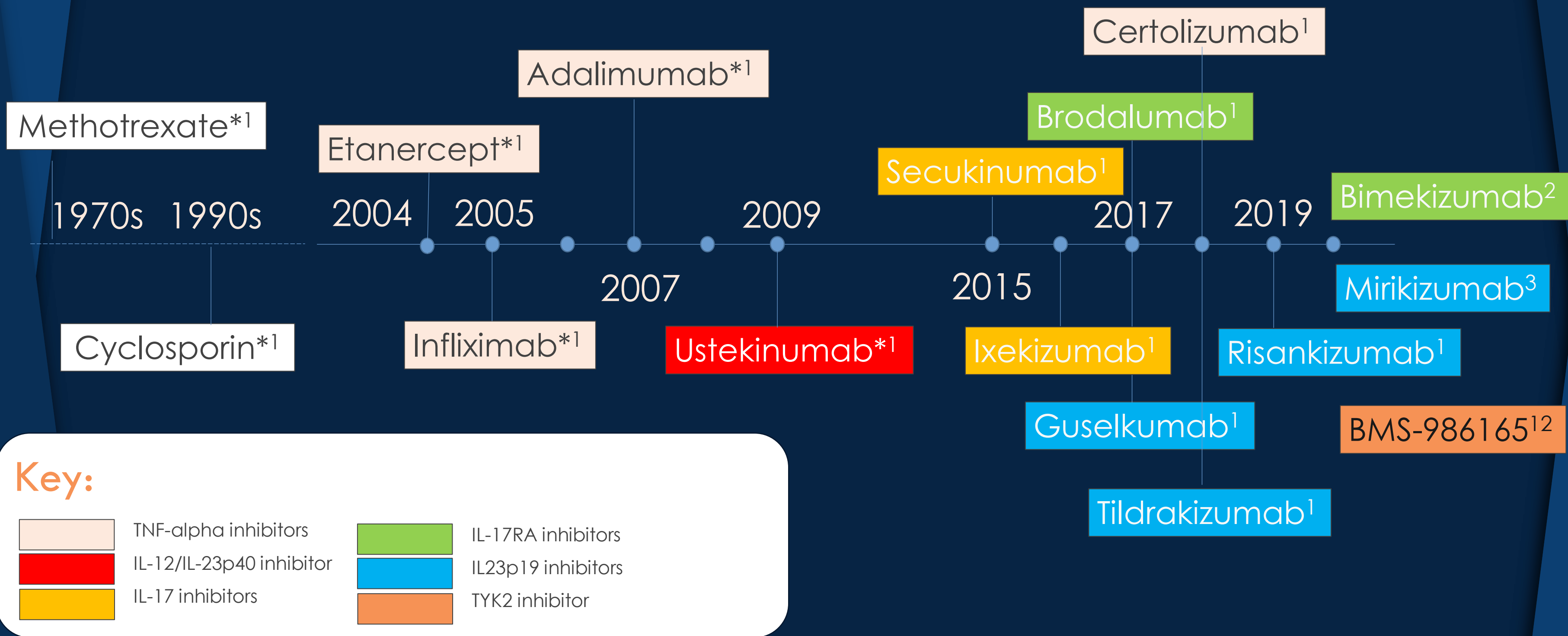
The lines represent the percentage of patients with 50% improvement (orange solid), the percentage with 75% improvement (long dashed), the percentage with 90% improvement (short dashed) and the number of patients (light orange line)

BSA, Body Surface Area; LOCF, Last Observation Carried Forward; MTX, Methotrexate; PASI, Psoriasis Area and Severity Index; QoL, Quality of Life.

1. Menter et al J Am Acad Dermatol 2020;82:1445–86;

2. Van Geel MJ, et al. J Dermatol Treatment. 2015;26(5):406–12.

Evolving landscape in psoriasis treatment



* Currently recommended for treatment of psoriasis in pediatric patients⁴

1. FDA-Approved Drugs. Available at: <https://www.accessdata.fda.gov/scripts/cder/daf/> (accessed September 2020); 2. ClinicalTrials.gov. Available at: <https://clinicaltrials.gov/ct2/show/NCT04036435> (accessed September 2020);

3. ClinicalTrials.gov. Available at: <https://clinicaltrials.gov/ct2/show/NCT03535194> (accessed September 2020); 4. ClinicalTrials.gov. Available at: <https://www.clinicaltrials.gov/ct2/show/NCT03536884> (accessed September 2020);

4. Menter A, et al. J Am Acad Dermatol. 2020;82(1):161-201

Biologics offer greater improvements in PASI vs. MTX

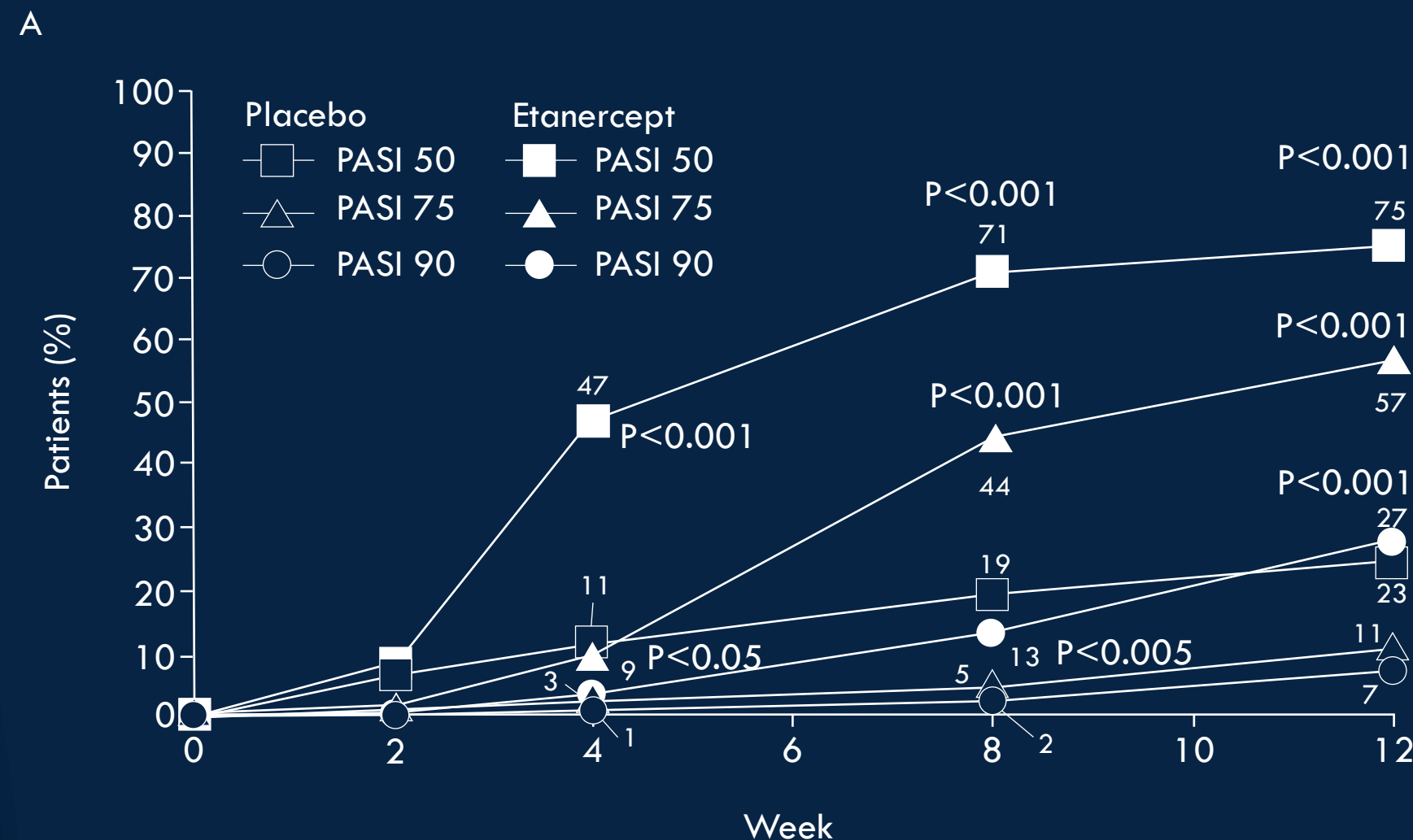
- ▶ Patients receiving biologics more likely to achieve PASI 75 vs. MTX
- ▶ Patients receiving biologics also more likely to achieve PGA status of clear or almost clear vs. MTX
- ▶ Biologics also associated with higher drug survival rates at 1, 3, and 5 years, with comparable discontinuation rates to MTX due to lack of response

Table 3. Psoriasis Severity Through 6-Month Follow-up by Treatment for PGA and PASI

Treatment	PGA 0/1 ^{a,b,c}		PASI75 ^{a,b,c}		PGA Score ^{a,b,d}		PASI Score ^{a,b,d}	
	No. of Patients	OR (CI)	No. of Patients	OR (CI)	No. of Patients	Effect (SD)	No. of Patients	Effect (SD)
Methotrexate	135	1 [Reference]	36	1 [Reference]	135	0 [Reference]	36	0 [Reference]
Biologic	42 ^e	2.00 90.98 to 4.00)	34 ^f	4.56 (2.02 to 10.27)	42 ^e	-0.31 (-0.56 to -0.06)	34 ^f	-3.13 (-4.33 to -1.94)
P Value		.06		<.001		.02		<.001

Etanercept treatment for children and adolescents with plaque psoriasis

Proportions of patients with improvements over baseline in the PASI



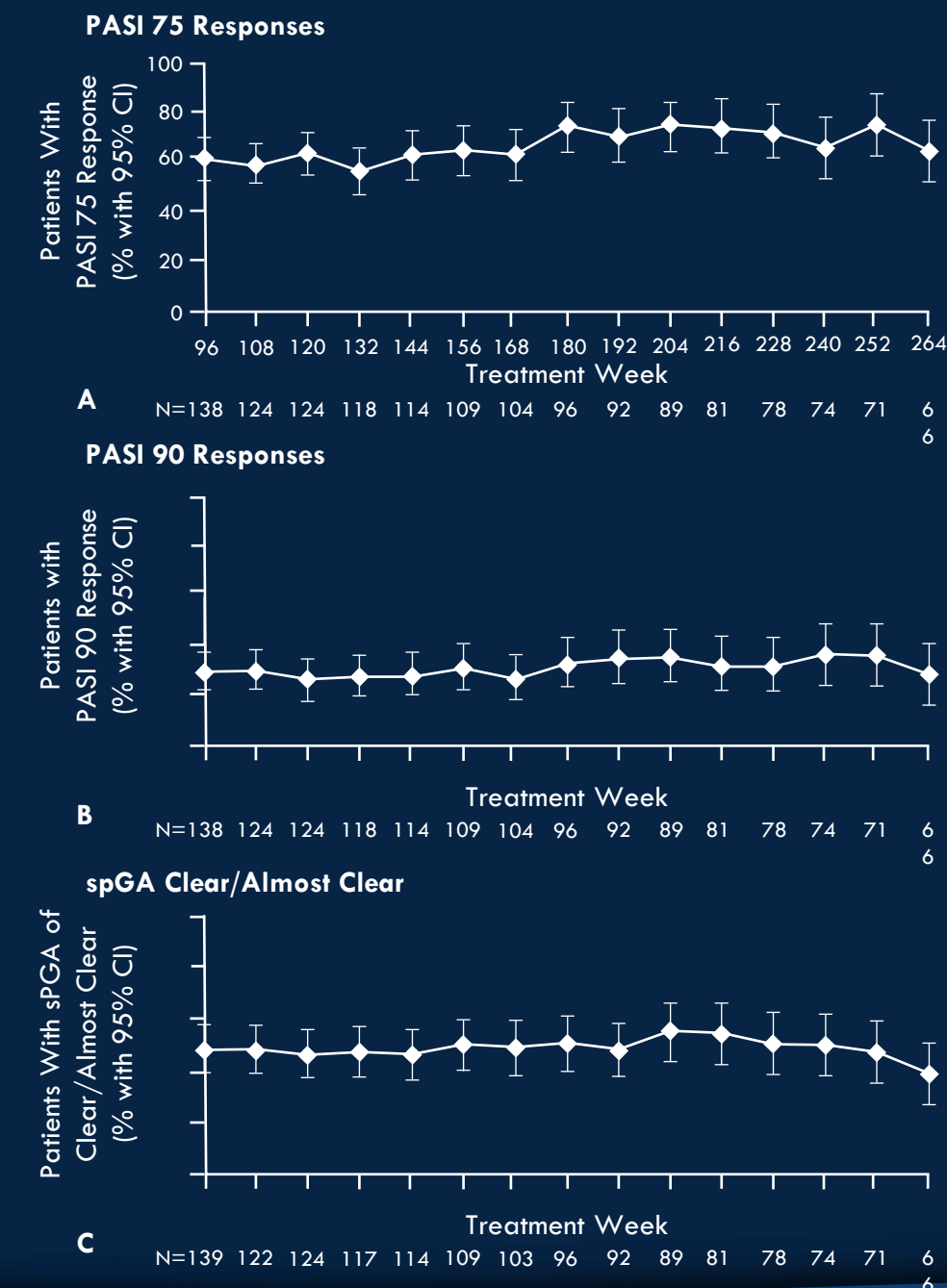
- ▶ At Week 12, significantly higher proportion of etanercept vs. placebo patients achieved PASI 75 (57% vs. 11%, $p<0.001$) and PASI 90 (27% vs. 7%, $p<0.001$)
 - ▶ Further improvements at Week 36, (after 24 weeks of open-label etanercept)
 - ▶ 68% and 65% of patients initially assigned to etanercept and placebo achieved PASI 75, respectively
- ▶ During withdrawal period, response was lost by 42% patients assigned to placebo at second randomisation

Etanercept significantly reduced disease severity in children and adolescents with moderate to severe plaque psoriasis

Long-term efficacy and safety of etanercept in children and adolescents with plaque psoriasis

- ▶ 182 patients enrolled in the long-term extension of double-blind trial¹
- ▶ Etanercept efficacy maintained for up to 264 weeks¹
 - ▶ PASI 75 achieved in ~60–70%
 - ▶ PASI 90 achieved in ~30%–40%
 - ▶ Static physician global assessment status clear/almost clear in ~40%–50%
- ▶ Cellulitis (n=1), no malignancy, no deaths¹
- ▶ Serum levels and efficacy similar in patients with (16%) and without anti-etanercept antibodies²

Plaque psoriasis, efficacy outcomes in children and adolescents treated with etanercept¹



Efficacy of adalimumab vs. MTX in paediatric patients with plaque psoriasis

- ▶ Adalimumab 0.8 mg/kg provides greater efficacy than MTX in children and adolescents with severe plaque psoriasis
- ▶ At Week 16:
 - ▶ Significantly more patients achieved PASI 75 vs. MTX
 - ▶ Higher proportions achieved PASI 90 and PASI 100
 - ▶ Improvements in CDLQI numerically higher
 - ▶ Improvements in PedsQL exceeded minimal clinically important difference

Week 16	MTX (n=37)	Adalimumab 0.4 mg/kg (n=39)	Adalimumab 0.8 mg/kg (n=38)	P*
PASI 75, n (%)	12 (32)	17 (44)	22 (58)	0.027
PASI 90, n (%)	8 (22)	12 (31)	11 (29)	0.466
PASI 100, n (%)	1 (3)	4 (10)	7 (18)	0.056
CDLQI change from baseline, mean (SD) †	-5.0 (7.1)	-4.9 (6.2)	-6.6 (6.2)	0.304
PedsQL, change from baseline, mean (SD) ¶	1.9 (10.4)	9.5 12.3	10.8 (15.4)	0.005

*Adalimumab 0.8 mg/kg versus methotrexate; †Scores range from 0 to 30, with higher scores indicating worse impairment of quality of life. A higher proportion of patients assigned to adalimumab 0.8 mg/kg achieved the minimum clinically important difference of ≥ 2.5 for CDLQI compared with methotrexate (26 [68%] vs 22 [59%]) or adalimumab 0.4 mg/kg (23 [59%], $p=0.419$). ‡n=36. §n=38. ¶ Scores range from 0 to 100, with higher scores indicating better health-related quality of life; Scores range from 0 to 100, with higher scores indicating better health-related quality of life. A higher proportion of patients assigned to adalimumab 0.8 mg/kg achieved the minimum clinically important difference of ≥ 4.36 for PedsQL compared with methotrexate (23 [61%] vs 16 [43%]) or adalimumab 0.4 mg/kg (21 [54%], $p=0.134$).

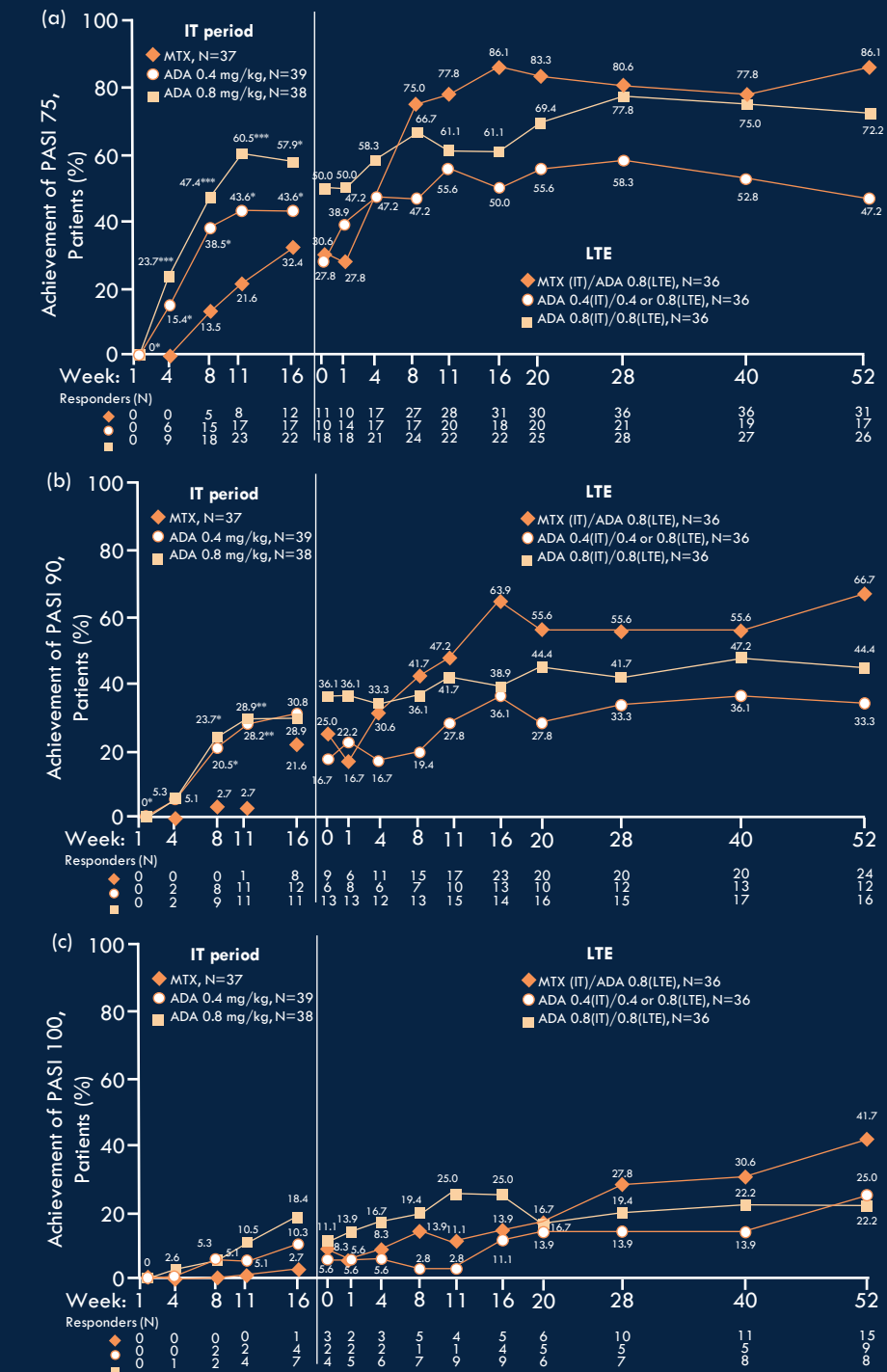
CDLQI, Children's Dermatology Life Quality Index; PASI75/90/100, at least 75%/90%/100% improvement from baseline in Psoriasis Area and Severity Index score; PedsQL, Paediatric Quality of Life Inventory.

Papp K, et al. *Lancet*. 2017;390(10089):40–49

Long-term efficacy of adalimumab in paediatric patients with severe plaque psoriasis

Percentage achieving PASI 75/ PASI 90/ PASI 100*¹

- ▶ Disease severity reduced/maintained or further improved after 52 weeks adalimumab 0.8 mg/kg treatment in children aged 4–18 years with severe plaque psoriasis¹
 - ▶ Treatment response (PASI 75, PASI 90 and PASI 100) improved for all efficacy groups from the start of the LTE across 52 weeks of treatment
 - ▶ Highest response rates with MTX (IT)/ADA 0.8 mg/kg (LTE) at Week 52¹
- ▶ No new safety signals identified in the treatment of paediatric patients with adalimumab^{1,2}
 - ▶ 0.8% of paediatric psoriasis develop serious infections²



* Of 114 patients randomised, 108 entered the LTE period.

ADA, Adalimumab; IT, Initial Treatment; LTE, Long-Term Extension; MTX, Methotrexate; PASI 75/90/100, at least 75%/90%/100% improvement from baseline in Psoriasis Area and Severity Index score.

1. Thaci D, et al. *British J Dermatol.* 2019;181(6):1177–1189; 2. Horneff G, et al. *J Peds* 2018;201:166–175.

Efficacy of ustekinumab in adolescents with moderate-to-severe plaque psoriasis (CADMUS)

- ▶ Robust and clinically meaningful improvements in disease activity with ustekinumab in adolescents (12–17 years)
 - ▶ At Week 12, significantly greater proportions of ustekinumab vs. placebo patients achieved PASI 75 and PASI 90 ($p < 0.001$)
- ▶ Significantly greater improvements in HRQoL with ustekinumab vs. placebo group

Week 12	Placebo (n=37)	Ustekinumab HSD (n=37)	Ustekinumab SD (n=36)
PASI 75, n (%)	4 (10.8)	29 (78.4)*	29 (80.6)*
PASI 90, n (%)	2 (5.4)	20 (54.1)*	22 (61.1)*
CDLQI change from baseline, mean (SD)	-1.5 (3.2)	-5.6 (6.4) [†]	-6.7 (5.6)*
Patients with CDLQI 0/1, n (%)	4/30 (13.3)	12/31 (38.7) [‡]	17/30 (56.7)*

Ustekinumab provides an alternative mode of action to the currently approved biologics for the treatment of psoriasis in children

* $p < 0.001$ vs. placebo; [†] $p < 0.01$ vs placebo; [‡] $p < 0.05$ vs placebo

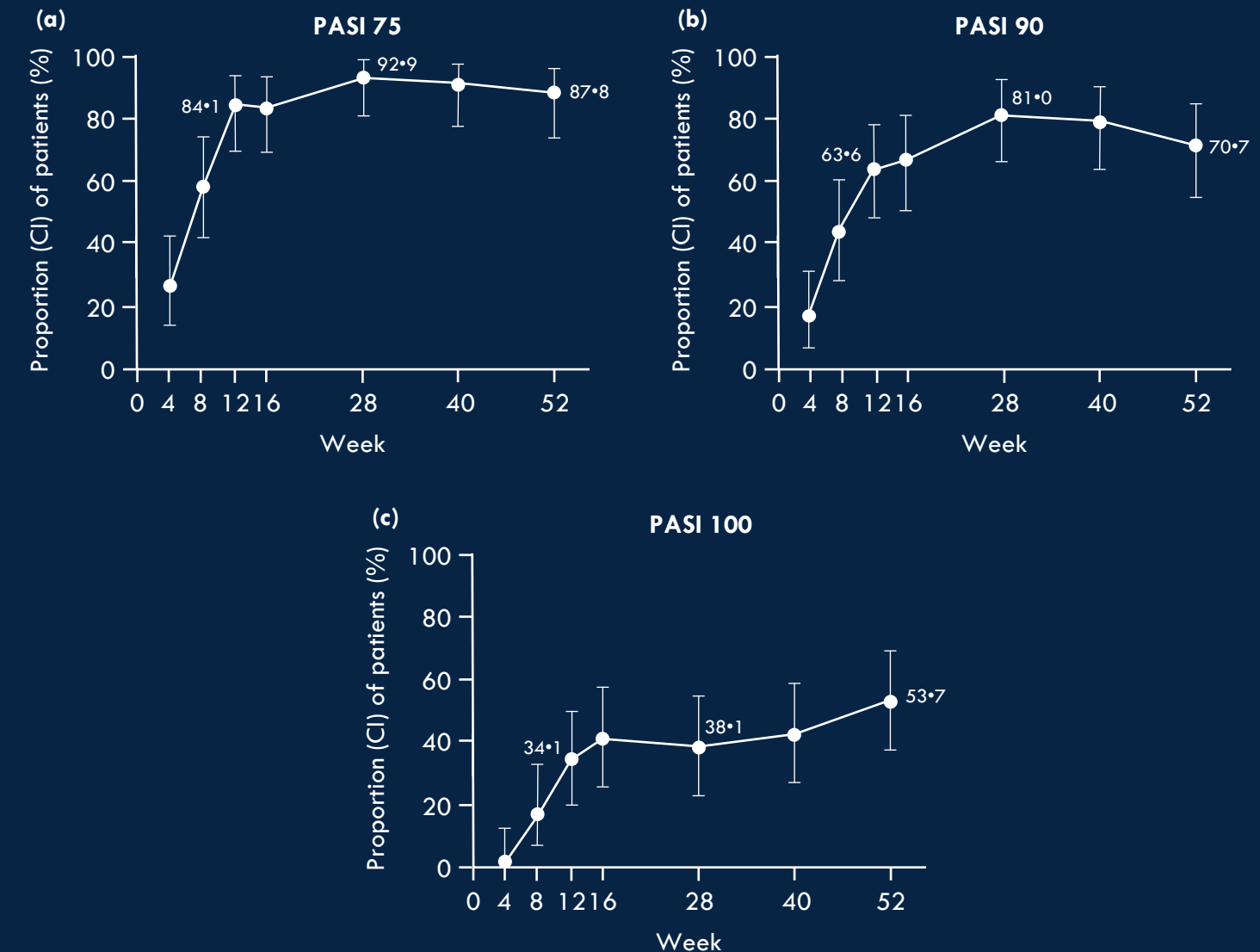
CDLQI, Children's Dermatology Life Quality Index; HRQoL, health related quality of life; HSD, half standard dosing; PASI75/90/100, at least 75%/90%/100% improvement from baseline in Psoriasis Area and Severity Index score; SD, standard dosing (0.75 mg/kg ≤ 60 kg; 45 mg/kg > 60 to ≤ 100 kg; 90 mg/kg > 100 kg).

Landells I, et al. *J Am Acad Dermatol.* 2016; 73(4):594–603

Efficacy of ustekinumab in paediatric patients with moderate-to-severe plaque psoriasis (CADMUS Jr)

- ▶ Ustekinumab effective in paediatric patients (6–11 years) with moderate-to-severe psoriasis in patients with no new safety signals
 - ▶ Efficacy maintained through 1 year
- ▶ Improvements in clinical measures of psoriasis accompanied by improvements in HRQoL
 - ▶ Majority of patients treated with ustekinumab achieved CDLQI of 0/1 at Week 12 (62%) and Week 52 (58%)

Proportions of patients achieving PASI 75, PASI 90 and PASI 100



Efficacy of ixekizumab in paediatric patients with moderate-to-severe plaque psoriasis (IXORA-PEDS)

- ▶ Ixekizumab superior to placebo in the treatment of paediatric patients (6–<18 years) with moderate-to-severe psoriasis
 - ▶ At Week 12, significantly greater proportions of ixekizumab vs. placebo patients achieved PASI 75, PASI 90 and PASI 100 ($p < 0.001$)
 - ▶ Clinically meaningful improvements over placebo persisted for up to 48 weeks
- ▶ Significantly greater improvements in HRQoL with ixekizumab vs. placebo group
- ▶ Safety profile consistent with that in adults

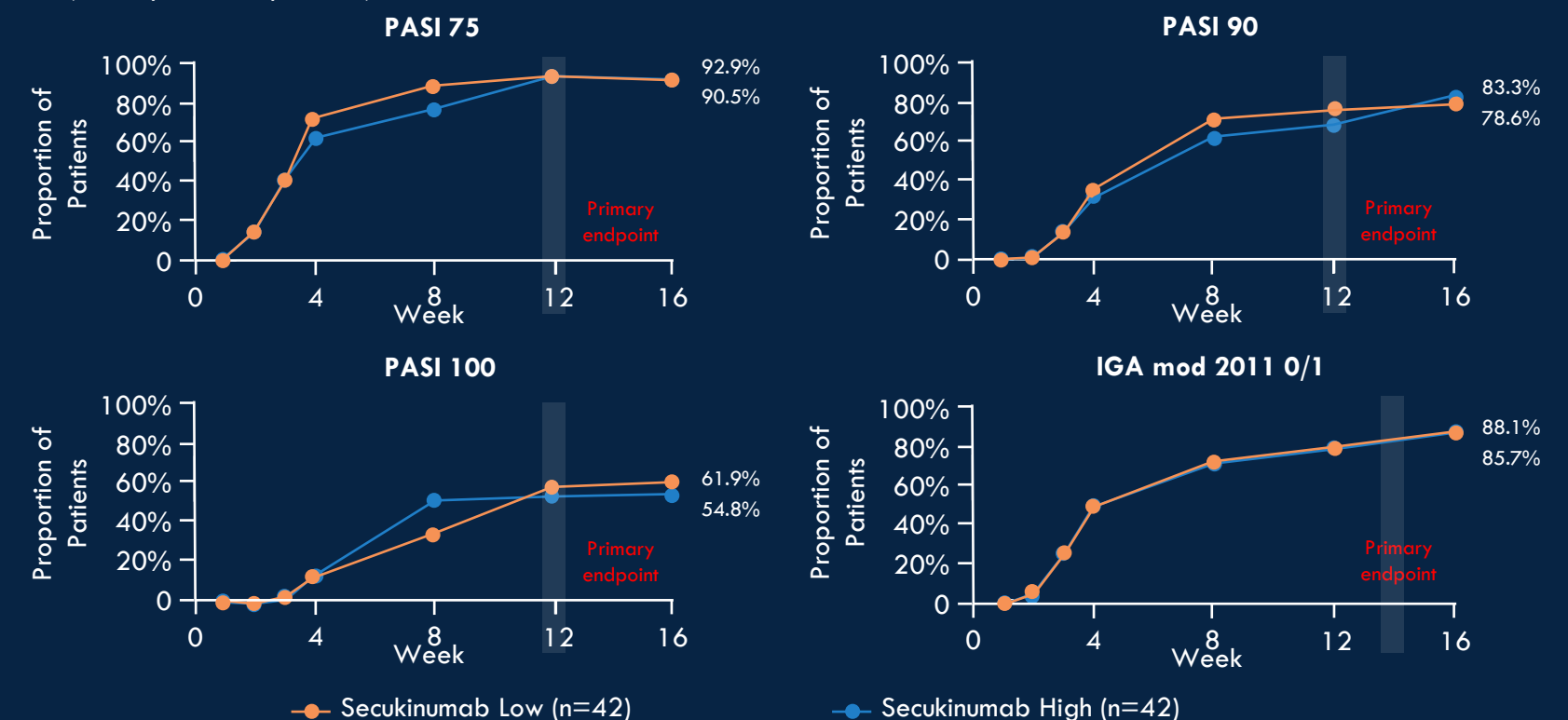
Week 12	Placebo (n=56)	Ixekizumab (n=115)	P-value
PASI 75, n (%)	14 (25)	102 (89)	<0.001
PASI 90, n (%)	3 (5)	90 (78)	<0.001
PASI 100, n (%)	1 (2)	57 (50)	<0.001
CDLQI/DLQI 0/1, n (%)	13 (23)	74 (64)	<0.001

Ixekizumab selectively targets IL-17A

Efficacy of secukinumab in paediatric patients with moderate-to-severe plaque psoriasis

- ▶ Secukinumab highly efficacious in rapidly improving skin symptoms and QoL in children and adolescents (6–<18 years) with moderate-to-severe plaque psoriasis
 - ▶ At Week 12, PASI 75, PASI 90 and PASI 100 was achieved by 93%, 69% and 60% of patients with low dose secukinumab, respectively
 - ▶ Majority (~50%) of patients treated with secukinumab achieved IGA of 0/1 at Week 12

Figure 1: Efficacy as measured by PASI75, PASI90, PASI100, and IGA mod 2011 0/1 through week 15 among pediatric patients with psoriasis (nonresponder imputation)



Secukinumab is a fully human mAb that selectively targets IL-17A

Emerging biologics

Biologics in Phase 3 clinical trials in paediatric patients with moderate-to-severe psoriasis

Agent	Target	Phase	NCT number	Trial	Age	Status
Guselkumab¹	IL-23	3	NCT03451851	PROTOSTAR	6-17 years	Recruiting
Tildrakizumab²	IL-23	3	NCT03997786		6-17 years	Recruiting
Risankizumab³	IL-23	3	NCT04435600		6-17 years	Recruiting
Certolizumab⁴	TNF-alpha	3	NCT04123795	CIMcare	6-17 years	Recruiting
Brodalumab^{5,6}	IL-17RA	3	NCT04305327	EMBRACE1	12-17 years	Not yet recruiting
		3	NCT03240809		6-18 years	Recruiting

IL-17RA, Interleukin-17 Receptor A; IL-23, interleukin-23; TNF-alpha, Tumour Necrosis Factor-alpha.

1. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT03451851>. Accessed September 2020;

2. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT03997786>. Accessed September 2020;

3. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT04435600>. Accessed September 2020;

4. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT04123795>. Accessed September 2020;

5. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT04305327>. Accessed September 2020;

6. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT03240809>. Accessed September 2020.

Apremilast in paediatric patients with moderate to severe plaque psoriasis: Phase 2

- ▶ No oral systemic treatment for moderate to severe psoriasis is approved for paediatric use
- ▶ Apremilast, an oral PD4i, is approved for the treatment of adults with moderate to severe plaque psoriasis or active psoriatic arthritis
- ▶ Phase 2 development in paediatric patients with moderate to severe plaque psoriasis
 - ▶ To evaluate pharmacokinetics and safety of apremilast in paediatric patients, with the primary aim of determining the paediatric doses for a Phase 3 study
 - ▶ This is the first study to evaluate apremilast in children with psoriasis (2–17 years)
- ▶ Promising exploratory efficacy endpoints:
- ▶ At Week 16, mean (SD) % change from baseline in PASI score
 - ▶ 69.6 (19.5) for adolescents treated with apremilast 20 mg bid
 - ▶ 66.5 (17.1) for adolescents treated with apremilast 30 mg bid
 - ▶ 79.3 (17.4) for children treated with apremilast 20 mg bid

What's wrong with Mia?

- ▶ As Mia* is approaching adolescence, a critical point in the development of emotional and psychosocial well-being, her parents and doctor are keen to keep trying new treatment options that could work for her



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Summary

- ▶ In the real world, the greatest improvements in QoL are associated with PASI 90 or higher¹
- ▶ Biologics are powerful and safe tools in the armamentarium of psoriasis treatment
- ▶ They offer greater improvements in paediatric psoriasis severity and higher drug survival than MTX in the real-world²
- ▶ This can allow patients like Mia to be in greater control of their psoriasis and able to lead a normal life

Panel discussion and live Q&A

Please use the chat function to enter your questions for the speakers

Click the link below to take our participant's evaluation form or scan the QR code



Thank you for your participation

For more information on Mia's story and to find additional educational content visit the **Improving treatment options for childhood psoriasis Learning Zone** on [Medthority.com](https://www.medthority.com)



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