



XXIII CONVEGNO NAZIONALE

DERMATOLOGIA PER IL PEDIATRA

*La terapia...
un dono grande*

26-27 Maggio 2023

Palazzo dei Congressi, Riccione

Quando e come utilizzare i monoclonali

Andrea Conti

SC Dermatologia – Ospedale Infermi di Rimini, AUSL Romagna

andrea.conti@auslromagna.it

CONFLITTO DI INTERESSI

Io sottoscritto Andrea Conti dichiaro che ho avuto rapporti di finanziamento con i seguenti soggetti portatori di interessi commerciali in ambito sanitario:

Abbot, Abbvie, Wyeth, Schering Plough, MDS, Janssen Cilag, Celgene, Eli Lilly, Novartis, Leo Pharma, UCB, Almirall, Sandoz, Pfizer, Biogen, Boehringer Ingelheim, Alfasigma.

Approccio terapeutico in età pediatrica con farmaci biologici



- Psoriasi moderata/grave



- Dermatite atopica



- Orticaria cronica spontanea (CSU)

Psoriasi: epidemiologia

- Prevalenza nella popolazione pediatrica: 1%
- L'incidenza della malattia è costantemente in crescita dal 1970 ad oggi
- 4.1% di tutte le dermatosi osservate al di sotto i 16 anni
- 1/3 dei pazienti ha le prime manifestazioni in età pediatrica
- 27% riportano l'insorgenza prima dell'età di 16 anni
- 2% prima dei 2 anni
- Età media alla prima diagnosi: 10.6 anni



Psoriasi: caso clinico

- Luca: 8 anni
- Psoriasi grave dall'infanzia
- Terapie effettuate:
 - Corticosteroidi topici e sistemici
 - Tacrolimus
 - Fototerapia UVBTL01
 - Ciclosporina A
 - Retinoidi

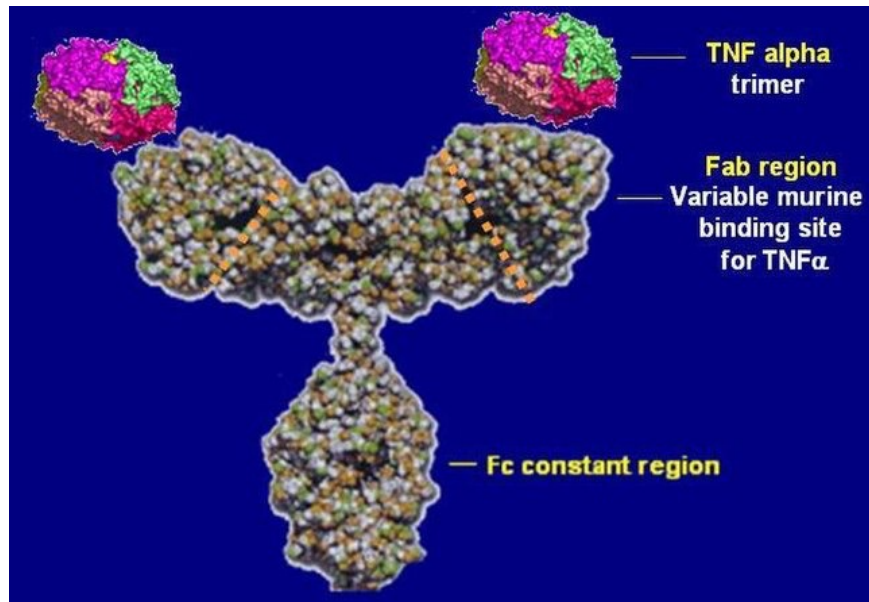
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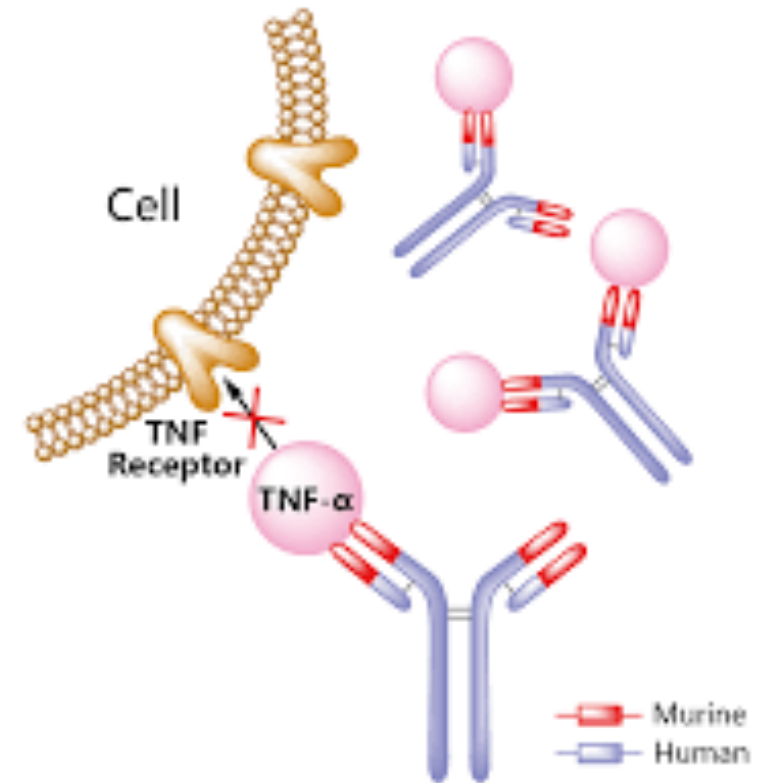


Psoriasis suberitrodermica

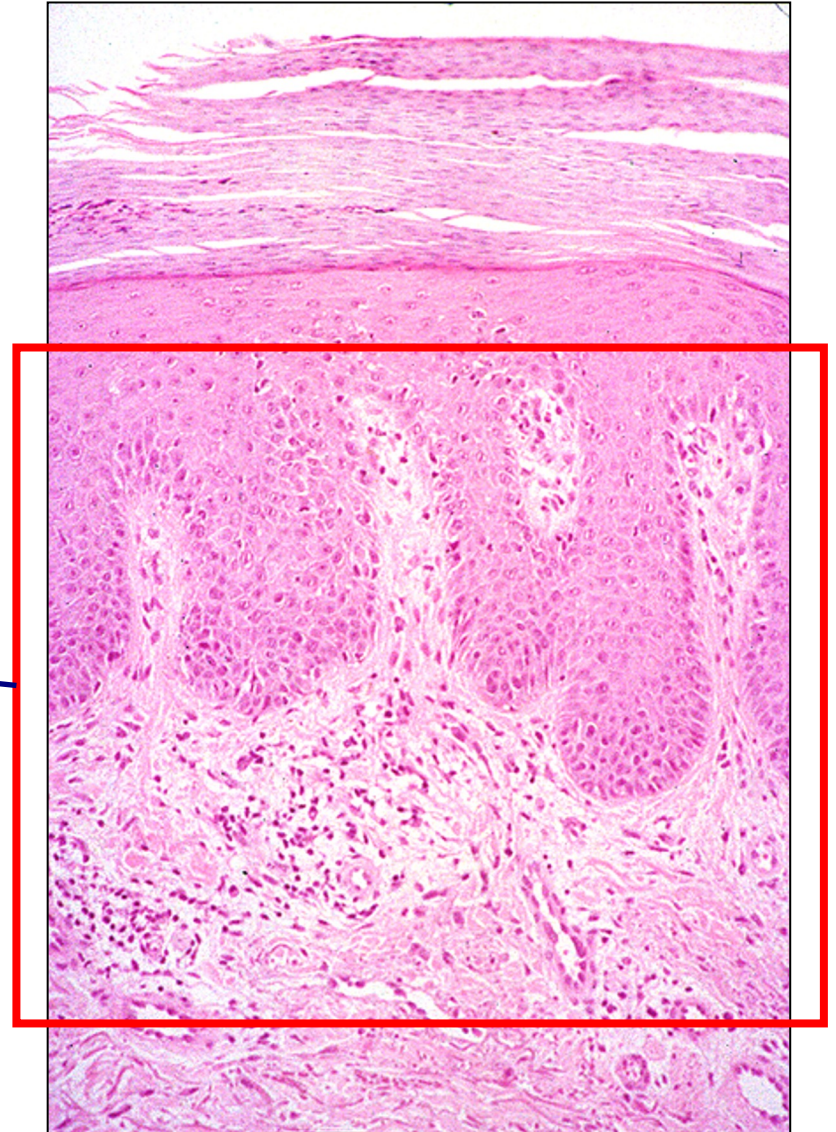
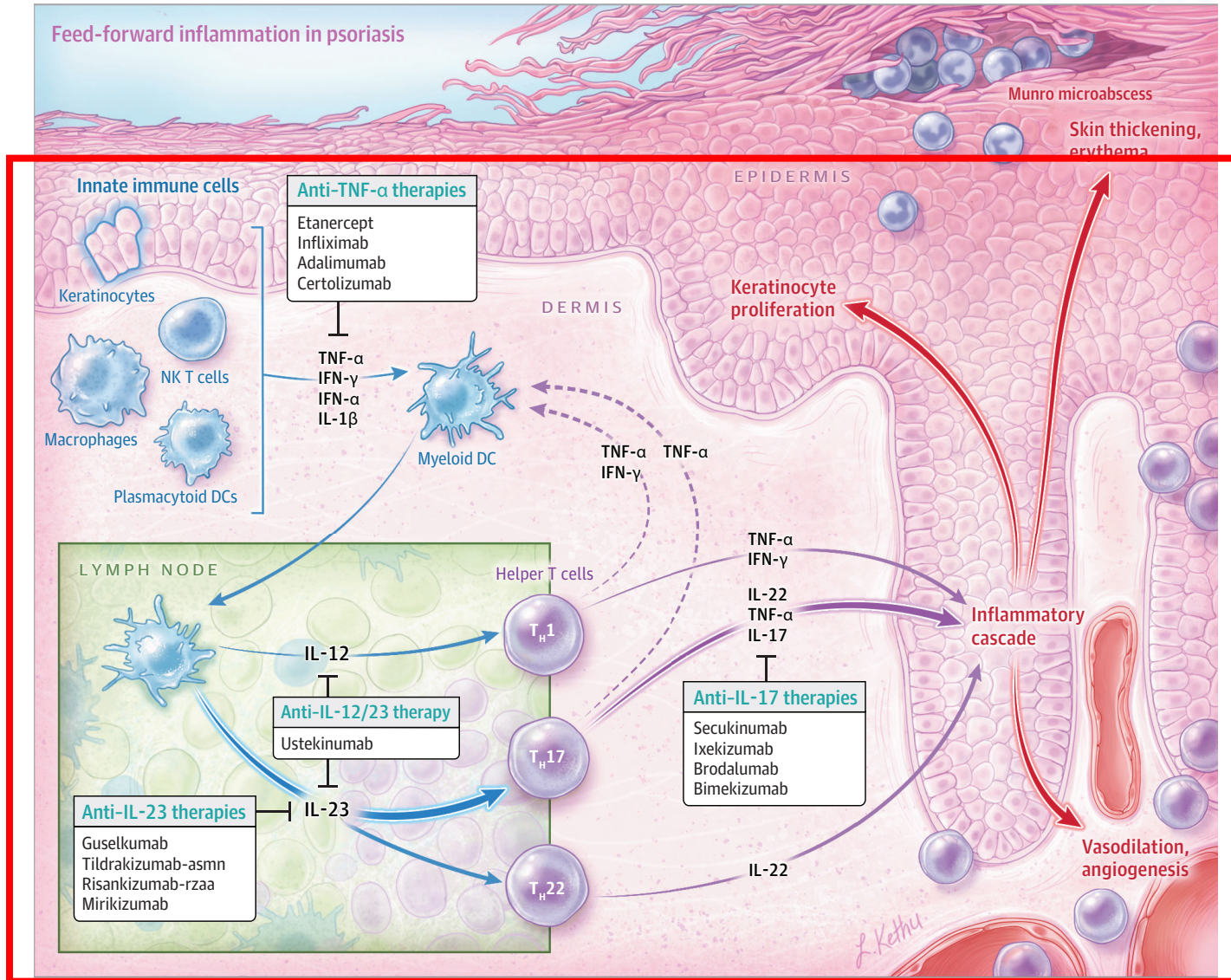
Scelta terapeutica

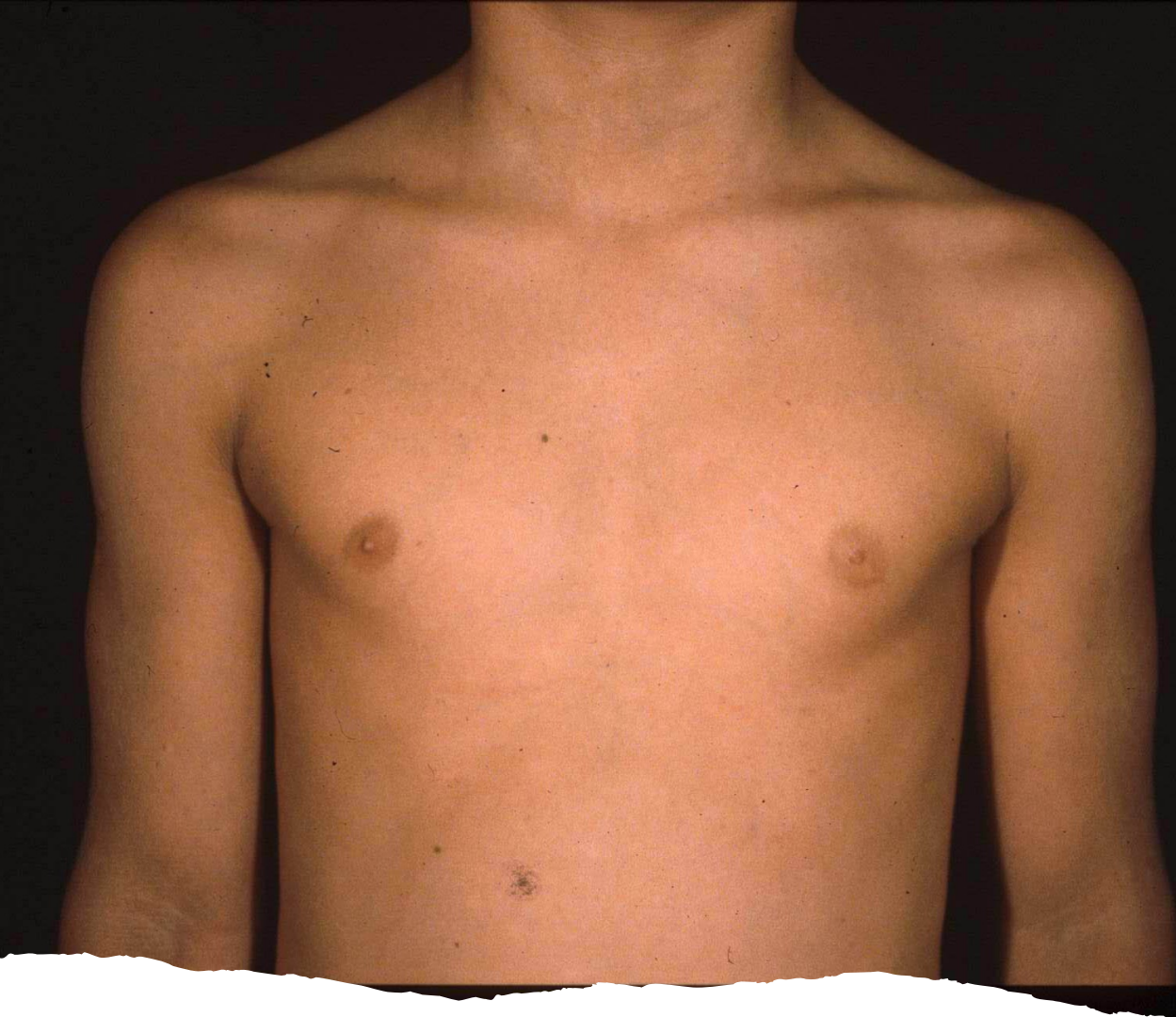


Infliximab (anti TNF-alfa) 5 mg/Kg e.v.



Patogenesi della psoriasi





Dopo 6 mesi tp con IFX



Dopo 2 anni di tp con IFX

**Trattamento sistemico
della psoriasi cronica
a placche moderata-grave*****Etanercept
nel trattamento della
psoriasi in età pediatrica****Aggiornamento Febbraio 2012*

A cura del gruppo di lavoro multidisciplinare
sui Farmaci Biologici in Dermatologia
Regione Emilia-Romagna

RACCOMANDAZIONE

Sulla base dei dati disponibili e alla stregua di quanto deciso per la psoriasi a placche dell'adulto, il gruppo di lavoro concorda che nella psoriasi cronica a placche del bambino il trattamento con etanercept possa essere considerato quando tutte le seguenti condizioni siano soddisfatte:

- età > 6 anni;
- presenza di PASI >20 o BSA >20% oppure PASI fra 10 e 20 e CDLQI >10 associato a lesioni al viso o palmari/plantari, ungueali o genitali;
- mancata risposta, intolleranza o controindicazione a MTX;
- mancata risposta, intolleranza o controindicazione a ciclosporina;
- mancata risposta, intolleranza o controindicazione ad acitretina (se <12 anni);
- mancata risposta, intolleranza o controindicazione a PUVA terapia (se >12 anni).

Per la gestione dell'etanercept in termini di indicazioni, controindicazioni e avvertenze d'uso fare riferimento al documento regionale: *"Trattamento sistemico della psoriasi cronica a placche moderata-grave"* - Linee Guida Terapeutiche/1.

Il documento è stato prodotto dal gruppo di lavoro multidisciplinare in dermatologia RER e approvato dalla Commissione Terapeutica Regionale.

Composizione del gruppo di lavoro

Dermatologi: Di Lernia V. (Azienda Ospedaliera di Reggio Emilia), Di Nuzzo S. (Azienda Ospedaliera - Universitaria di Parma), Lasagni C. (Azienda Ospedaliera - Universitaria di Modena), Patrizi A. (Azienda Ospedaliera - Universitaria di Bologna), Virgili A.R. (Azienda Ospedaliera - Universitaria di Ferrara)

Metodologia e coordinamento: Magrini N. (CeVEAS, Centro per la Valutazione della Efficacia dell'Assistenza Sanitaria, Modena), Marata A.M. (CeVEAS, Centro per la Valutazione della Efficacia dell'Assistenza Sanitaria, Modena), Trombetta S. (Agenzia Sanitaria e Sociale Regionale)

Farmacisti: De Rosa M. (Azienda USL di Modena), Fiacchi Paola (Azienda Ospedaliera - Universitaria di Bologna), Pieraccini F. (Azienda USL di Forlì); Santachiara S. (Azienda Ospedaliera - Universitaria di Modena)

Direzione Sanitaria: Miselli Maurizio (Azienda Ospedaliera - Universitaria di Modena)

Assessorato alla Sanità Regione Emilia Romagna: Martelli L. (Servizio Politica del Farmaco), Carati D. (Servizio Politica del Farmaco), Sangiorgi E. (Servizio Politica del Farmaco)

TERAPIE BIOLOGICHE

(anti TNF-alfa, IL 12-23, IL 17, IL 23)

Biologic Therapies			
Class	Target	Generic name	Molecular Structure
TNF inhibitor	TNF- α	Etanercept	Receptor fusion protein
	TNF- α	Infliximab	Chimeric monoclonal antibody
	TNF- α	Adalimumab	Fully human monoclonal antibody
	TNF- α	Certolizumab peg	Fully human monoclonal antibody
IL-12/23 inhibitor	p40 subunit	Ustekinumab	Fully human monoclonal antibody
IL-17 inhibitor	IL-17a	Secukinumab	Fully human monoclonal antibody
	IL-17a	Ixekizumab	Humanized monoclonal antibody
	IL-17RA	Brodalumab	Fully human monoclonal antibody
IL-23 inhibitor	p19 subunit	Guselkumab	Fully human monoclonal antibody
	p19 subunit	Tildrakizumab	Humanized monoclonal antibody
	p19 subunit	Risankizumab	Humanized monoclonal antibody

Ciclosporina A

- Studi clinici hanno incluso bambini a partire da 1 anno di età in poi
- In diversi studi, i pazienti pediatrici hanno richiesto e tollerato dosi di ciclosporina per kg di peso corporeo più elevate di quelle usate negli adulti
- Ad eccezione del trattamento della sindrome nefrosica, non è disponibile una adeguata esperienza con ciclosporina
- L'uso nei bambini di età inferiore ai 16 anni in indicazioni diverse dal trapianto **non è raccomandato** ad eccezione della sindrome nefrosica



Effectiveness and safety of cyclosporine in pediatric plaque psoriasis: a multicentric retrospective analysis.

V. Di Lernia, L. Stingeni, V. Boccaletti, P.G. Calzavara Pinton, C. Guarneri, A. Belloni Fortina, M. Panzone, M. Corazza, I. Neri, S. Cambiaghi, C. Lasagni, E. Ficarelli, P. Gisondi

doi: 10.3109/09546634.2015.1120852

Abstract

Cyclosporine (CysA) is effective for psoriasis in adult patients but little data exist about its efficacy and safety in childhood and adolescence psoriasis.

Objectives. To assess the effectiveness and safety of CysA for childhood and adolescence psoriasis.

Methods. Retrospective analysis of a group of children and adolescents (age < 17 years) with plaque psoriasis treated with CysA at several Italian dermatology clinics.

Results. Our study population consisted of 38 patients. The median age at the start of treatment was 12,3 years. Therapy duration varied from 1 to 36 months. The median maintenance dosage per day was 3,2 mg/kg (range 2–5 mg/kg). Fifteen patients (39,4 %) achieved a complete clearance or a good improvement of their psoriasis defined by an improvement from baseline of $\geq 75\%$ in the Psoriasis Area and Severity Index at week 16. Eight patients (21.05%) discontinued the treatment due to laboratory anomalies or adverse events. Serious events were not recorded.

Conclusions. In this case series CysA was effective and well tolerated treatment in a significant quote of children. CysA, when carefully monitored, may represent a therapeutic alternative to the currently used systemic immunosuppressive agents for severe childhood psoriasis.

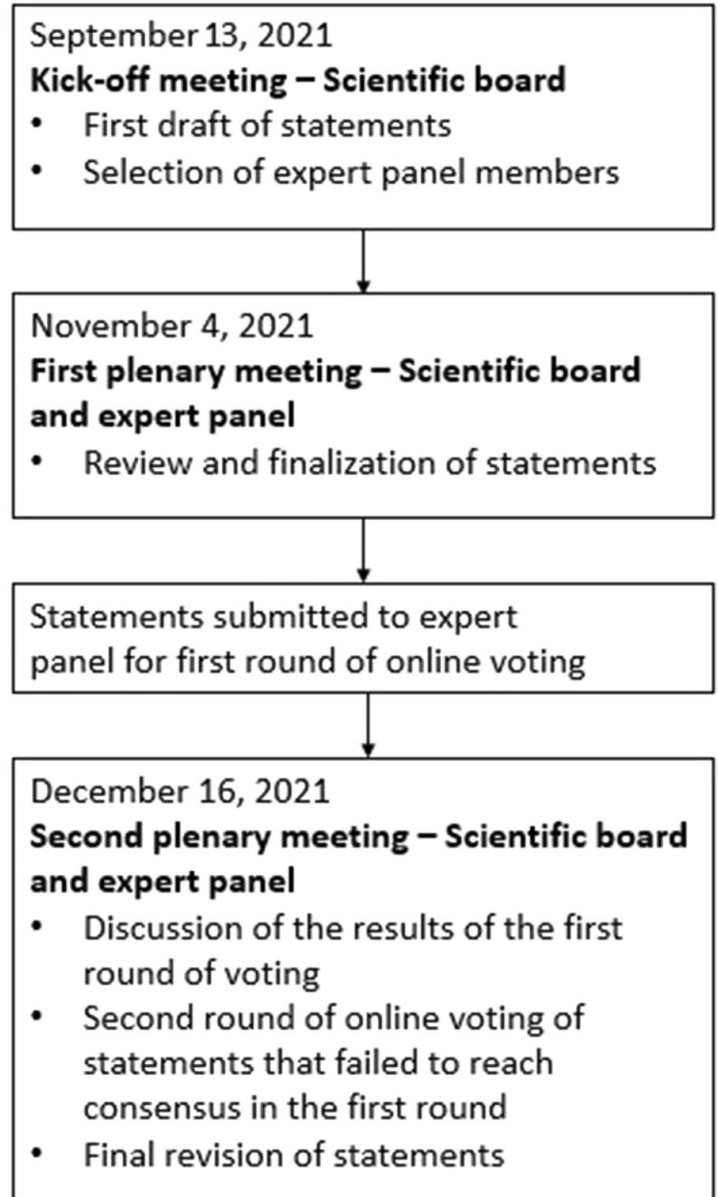


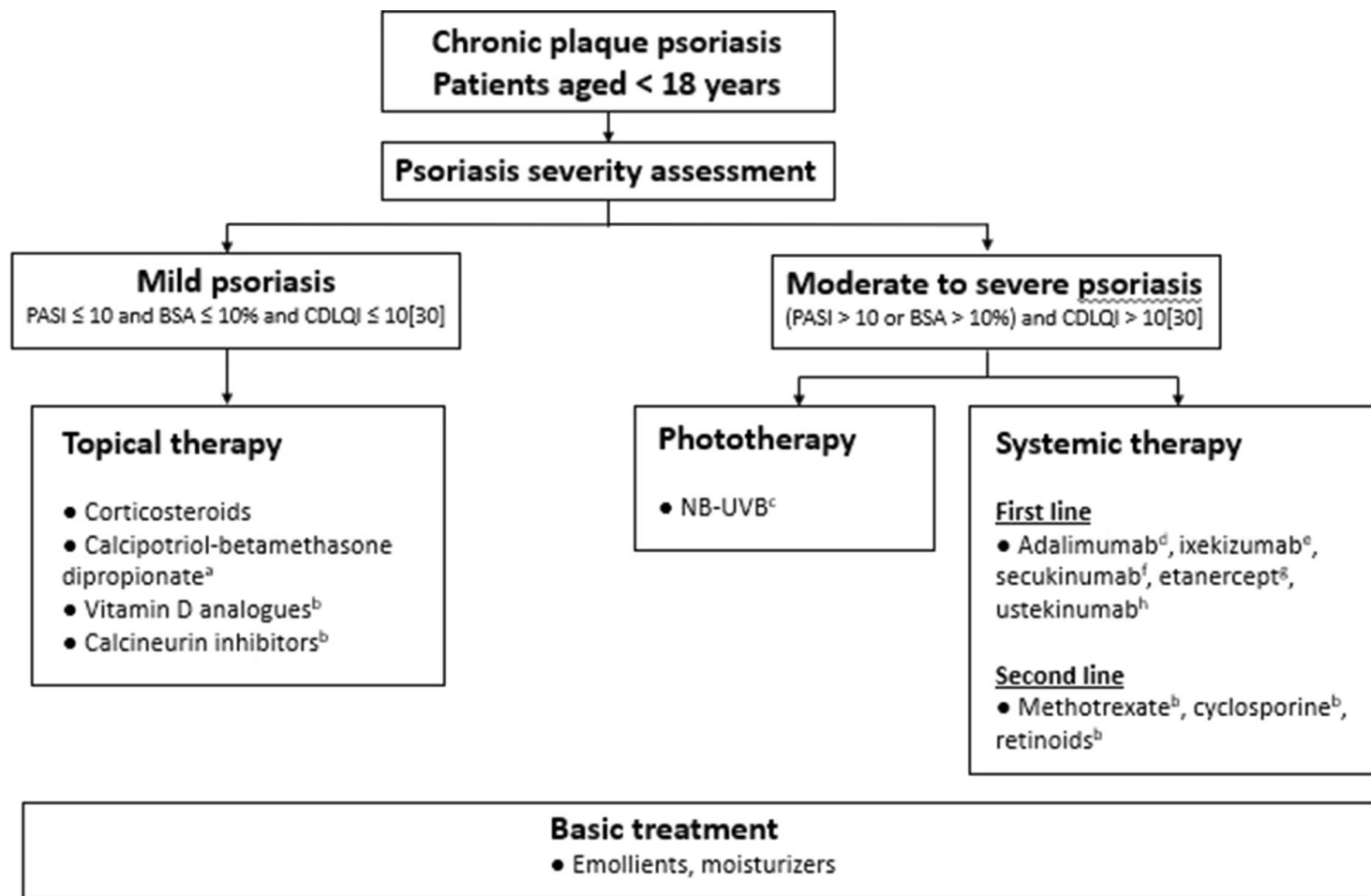
ORIGINAL RESEARCH

Update on the Management of Pediatric Psoriasis: An Italian Consensus

Ketty Peris · Anna Belloni Fortina · Luca Bianchi · Gabriella Fabbrocini · Paolo Gisoni ·
Anna Balato · Federico Bardazzi · Nicoletta Bernardini · Domenico Bonamonte · Maria Rita Bongiorno ·
Cinzia Buligan · Francesco Cusano · Maria Beatrice De Felici Del Giudice · May El Hachem ·
Maria Concetta Fargnoli · Giulio Gualdi · Claudio Guarneri · Katharina Hansel · Giovanna Malara ·
Carlo Mazzatenta · Giuseppe Micali · Alessandra Narcisi · Iria Neri · Teresa Oranges ·
Michele Panzone · Aurora Parodi · Lucia Restano · Oriana Simonetti · Marina Venturini ·
Vito Di Lernia 

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Systemic therapy—non-biologic options [19–21]

Methotrexate (off-label)	Oral or subcutaneous/intramuscular administration
	Usual dose: 0.2–0.7 mg/kg once weekly, up to 15 mg per week
	As soon as disease control is achieved (12–16 weeks), reduce gradually dose to lower maintenance regimen
	Daily folic acid (1–5 mg) recommended (except on day of methotrexate administration) to reduce side effects
Cyclosporine A (off-label)	Oral administration
	Initial dose: 2.5–5.0 mg/kg per day
	Optimal response expected after 8–16 weeks
	When disease is stable, slowly reduce to lowest effective dose
Retinoids (off-label)	Intermittent treatment courses are recommended
	Oral administration
	Initial acitretin dose: 0.3–0.5 mg/kg per day
	Maintenance dose: up to 1 mg/kg per day
	Improvement of skin lesions usually seen after 2–3 months of treatment
	Contraception recommended in female adolescents for up to 3 years from treatment discontinuation

Conventional systemic therapies are widely used in adults, but are not licensed in children

Anti TNF-alfa, anti IL17A, anti IL12-23

Non rimborsato AIFA!!

Adalimumab	Children aged 4–17 years Patient weight ≥ 15 kg and < 30 kg: initial dose of 20 mg SC, followed by 20 mg SC every other week Patient weight ≥ 30 kg: initial dose of 40 mg SC, followed by 40 mg SC every other week In non-responders, treatment beyond 16 weeks should be carefully considered
Ixekizumab	Children aged ≥ 6 years, with body weight ≥ 25 kg and for adolescents Patient weight 25–50 kg: start with 80 mg SC, followed by 40 mg SC every 4 weeks Patient weight > 50 kg: start with 160 mg SC (two 80 mg-injections), followed by 80 mg SC every 4 weeks
Secukinumab	Children aged ≥ 6 years Weekly dosing for 5 weeks, followed by monthly dosing for maintenance Body weight < 25 kg: 75 mg SC Body weight ≥ 25 kg and < 50 kg: 75 mg SC Body weight ≥ 50 kg: 150 mg SC (may be increased to 300 mg SC)
Etanercept	Children aged ≥ 6 years 25 mg twice weekly or 50 mg SC once weekly Alternatively: 50 mg SC twice weekly for up to 12 weeks, followed by 25 mg SC twice weekly, or 50 mg SC once weekly, if needed Treatment should be continued until remission, for up to 24 weeks Discontinue treatment if no response after 12 weeks
Ustekinumab	Children aged ≥ 6 years Administer at week 0 and 4, and then every 12 weeks Body weight < 60 kg: 0.75 mg/kg SC (table with injection volumes available in EMA label) Body weight ≥ 60 kg SC and ≤ 100 kg: 45 mg SC Body weight > 100 kg: 90 mg SC Discontinue treatment if no response after up to 28 weeks of treatment

TERAPIE BIOLOGICHE

(anti TNF-alfa, IL 12-23, IL 17, IL 23)

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TERAPIE BIOLOGICHE

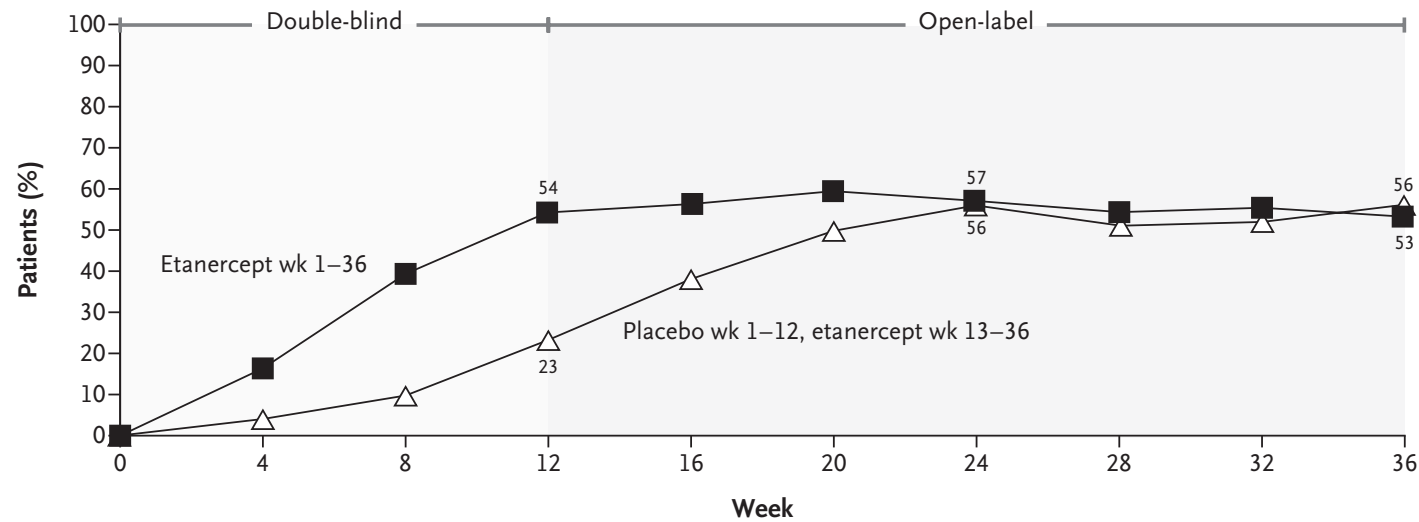
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	p19 subunit	Risankizumab	Humanized monoclonal antibody

ORIGINAL ARTICLE

Etanercept Treatment for Children and Adolescents with Plaque Psoriasis

Amy S. Paller, M.D., Elaine C. Siegfried, M.D., Richard G. Langley, M.D.,
Alice B. Gottlieb, M.D., Ph.D., David Pariser, M.D., Ian Landells, M.D.,
Adelaide A. Hebert, M.D., Lawrence F. Eichenfield, M.D.,
Vaishali Patel, Pharm.D., M.S., Kara Creamer, M.S.,
and Angelika Jahreis, M.D., Ph.D.,
for the Etanercept Pediatric Psoriasis Study Group*

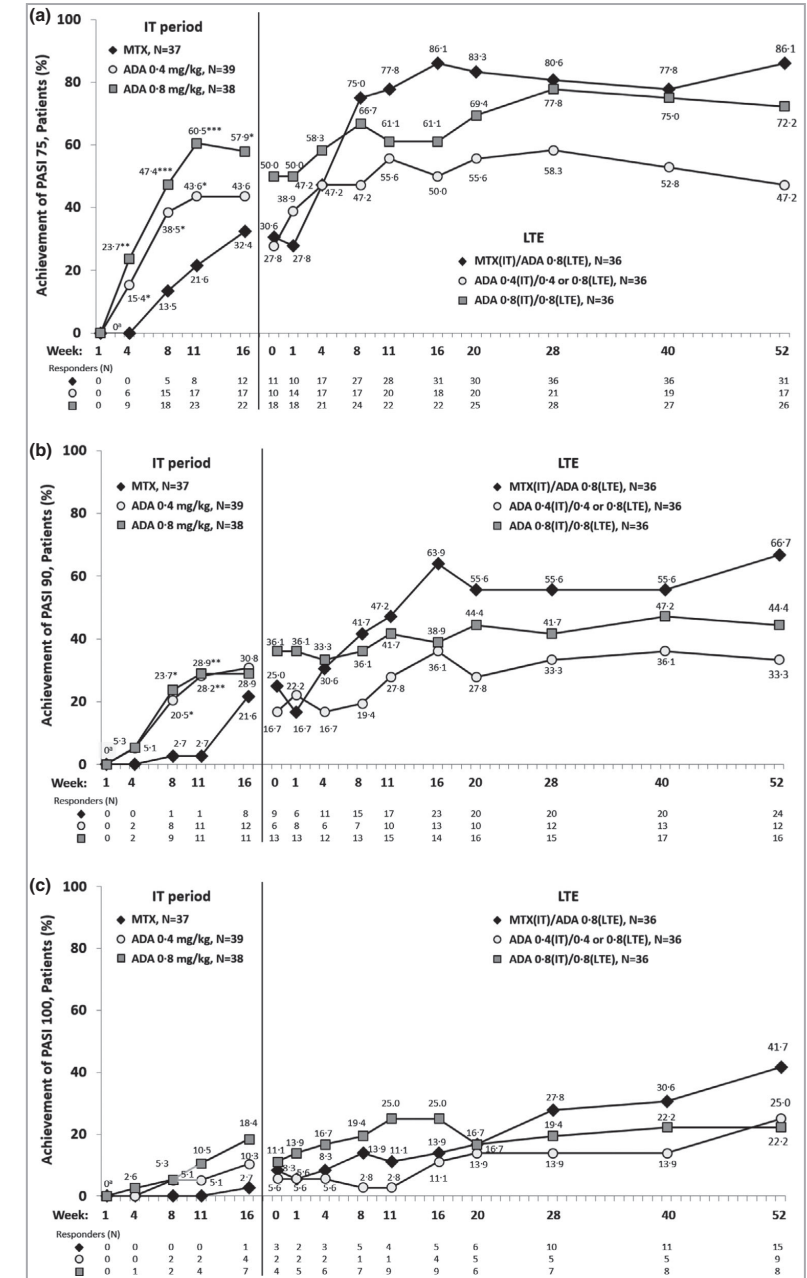


Sustained long-term efficacy and safety of adalimumab in paediatric patients with severe chronic plaque psoriasis from a randomized, double-blind, phase III study

D. Thaçi,¹ K. Papp,² D. Marcoux,³ L. Weibel,⁴ A. Pinter,⁵ P.-D. Ghislain,⁶ I. Landells,⁷ P.H. Hoeger,⁸ K. Unnebrink,⁹ M.M.B. Seyger,¹⁰ D.A. Williams,¹¹ S. Rubant⁹ and S. Philipp¹²

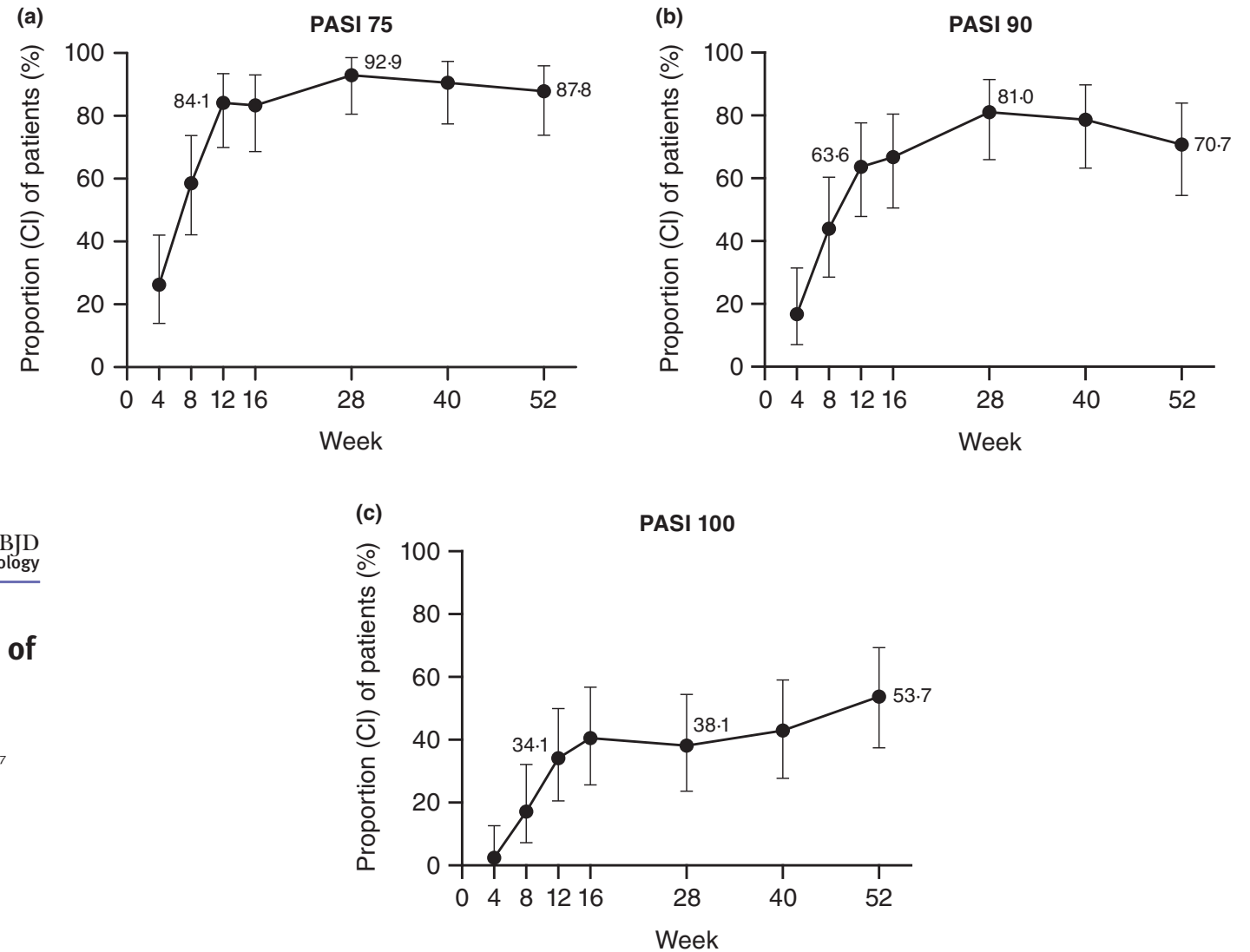
After 52 weeks of long-term ADA treatment in children aged 4–18 years with severe plaque psoriasis, **disease severity was reduced and maintained or further improved, as demonstrated by efficacy outcomes.**

No new safety risks were identified.



Ustekinumab for the treatment of moderate-to-severe plaque psoriasis in paediatric patients (≥ 6 to < 12 years of age): efficacy, safety, pharmacokinetic and biomarker results from the open-label CADMUS Jr study*

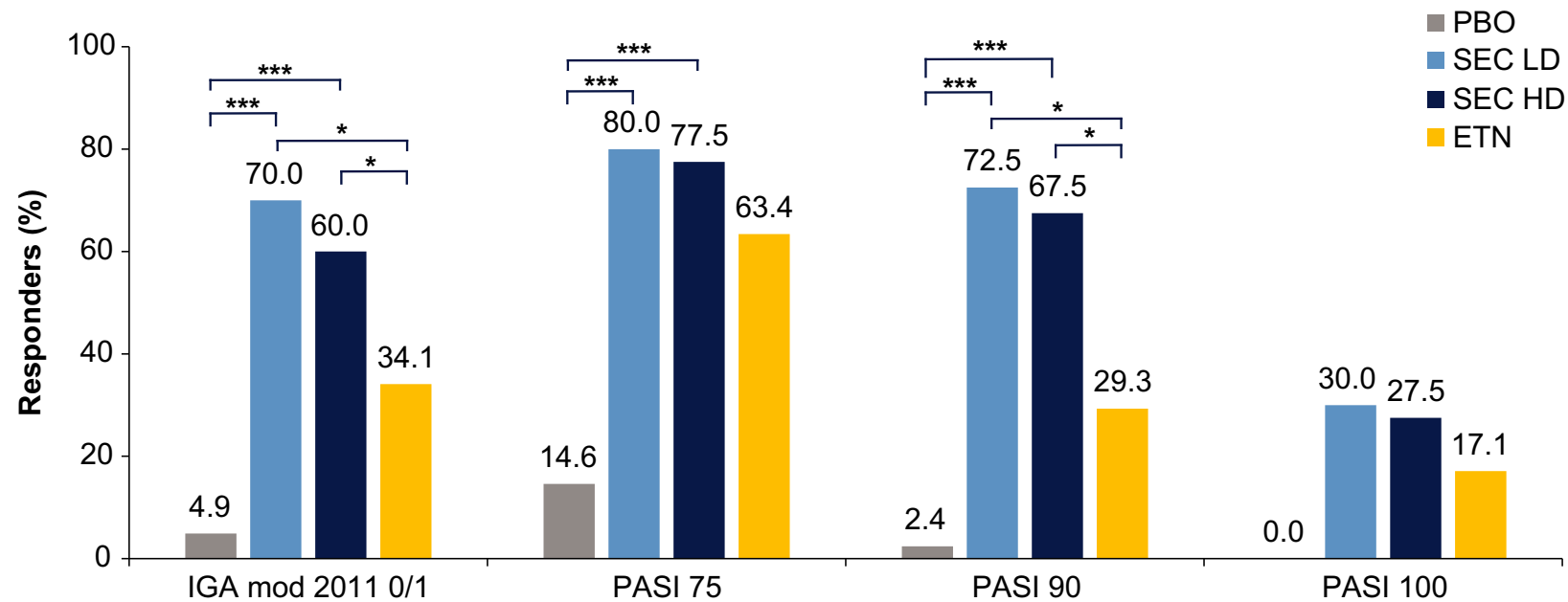
S. Philipp¹, A. Menter,² A.F. Nikkels,³ K. Barber,⁴ I. Landells,⁵ L.F. Eichenfield,⁶ M. Song,⁷ B. Randazzo,⁷ S. Li,⁷ M.-C. Hsu,⁷ Y. Zhu,⁷ S. DePrimo⁷ and A.S. Paller⁸



ORIGINAL ARTICLE

Secukinumab demonstrates high efficacy and a favourable safety profile in paediatric patients with severe chronic plaque psoriasis: 52-week results from a Phase 3 double-blind randomized, controlled trial

C. Bodemer,^{1,*} A. Kaszuba,² K. Kingo,³ A. Tsianakas,⁴ A. Morita,⁵ E. Rivas,⁶ P. Papanastasiou,⁷ D. Keefe,⁸ M. Patekar,⁷ P. Charef,⁷ L. Zhang,⁸ S. Cafoncelli,⁸ C. Papavassilis⁷



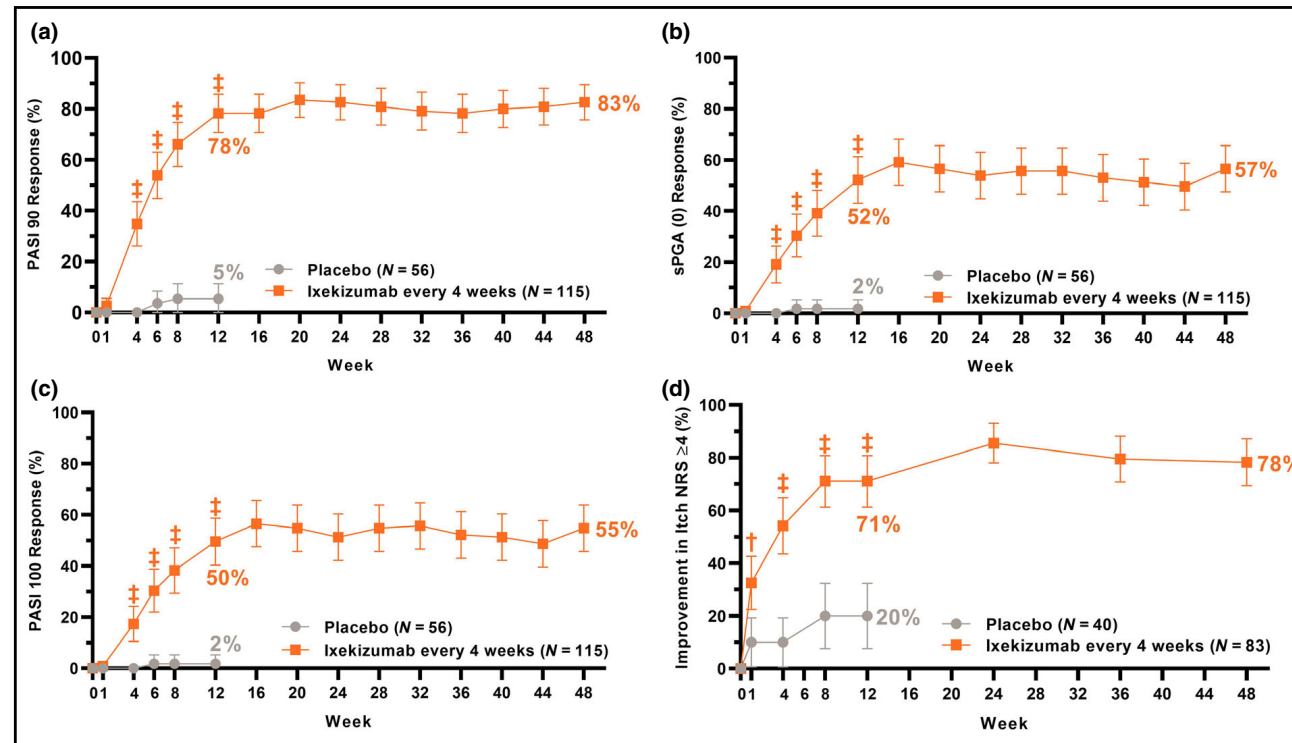
*** $P<0.0001$; * $P<0.05$

Efficacy and safety of ixekizumab in a phase III, randomized, double-blind, placebo-controlled study in paediatric patients with moderate-to-severe plaque psoriasis (IXORA-PEDS)*

A.S. Paller ¹, M.M.B. Seyger, ² G. Alejandro Magariños, ³ J. Bagel, ⁴ A. Pinter ⁵, J. Cather, ⁶ S. Keller, ⁷ C. Rodriguez Capriles, ⁷ R. Gontijo Lima, ⁷ G. Gallo, ⁷ C.A. Little, ⁷ E. Edson-Heredia ⁷, L. Li, ⁷ W. Xu, ⁷ and K. Papp ⁸ on behalf of the IXORA-PEDS study group

What does this study add?

- Ixekizumab resulted in rapid and statistically significant improvements over placebo in skin involvement, itch and health-related quality of life, which persisted through 48 weeks of treatment in paediatric patients with moderate-to-severe plaque psoriasis.
- The safety profile of ixekizumab was generally consistent with that seen in adults.
- Ixekizumab may be an additional potential therapeutic option and an additional class of biologic therapy (interleukin-17A antagonist) for the treatment of moderate-to-severe paediatric psoriasis.



Terapia sistemica: esperienza italiana

Treatment patterns with systemic antipsoriatic agents in childhood psoriasis: an Italian database analysis.

Vito DI LERNIA, Iria NERI, Piergiacomo CALZAVARA-PINTON, sergio DI NUZZO, Luca STINGENI, Claudio GUARNERI, Anna BELLONI FORTINA, Domenico BONAMONTE, stefano CAMBIAGHI, Claudia LASAGNI, michele PANZONE, Monica CORAZZA, Annamaria OFFIDANI, Paolo GISONDI

G Ital Dermatol Venereol 2016 Jan 13 [Epub ahead of print]

- 58 consecutive patients (27 males, 31 females).
- Median age at the start of the first systemic treatment: 11.7 y ($\pm$ 3.7).
- Most preferred first line systemic treatment:
 - **cyclosporine** (53.4% of patients)
 - **acitretin** (22.4% of patients)
 - **etanercept** and **PUVA** respectively (8.6%)
 - **methotrexate** (6.8%).
- 48.2% of patients received a second systemic treatment due to inefficacy or side effects of the first line therapy.

Treatment patterns with systemic antipsoriatic agents in childhood psoriasis: an Italian database analysis.

Vito DI LERNIA, Iria NERI, Piergiacomo CALZAVARA-PINTON, sergio DI NUZZO, Luca STINGENI, Claudio GUARNERI, Anna BELLONI FORTINA, Domenico BONAMONTE, stefano CAMBIAGHI, Claudia LASAGNI, michele PANZONE, Monica CORAZZA, Annamaria OFFIDANI, Paolo GISONDI

G Ital Dermatol Venereol 2016 Jan 13 [Epub ahead of print]

	Clinical remission *	Ineffectiveness	Side Effects	Other
Cyclosporin (n=38)	39.4%	39.4%	21.0%	0
Acitretin (n=18)	44.4%	44.4 %	5.5%	5.5%
Methotrexate (n=13)	7.6% (30.7%)	46.1 %	7.6%	7.6%
Etanercept (n=15)	33.3 % (20%)	46.6 %	0	0
PUVA (n=8)	25.0%	75.0%	0	0

Effectiveness and Safety of Adalimumab, Etanercept and Ustekinumab for Severe Psoriasis in Children Under 12 Years of Age: A French-Italian Daily Practice Cohort (BiPe Jr)

Jinane Zitouni, Alain Beauchet, Raphaëlle Curmin, Vito Di Lernia,
Anne-Claire Bursztejn, Juliette Mazereeuw-Hautier, Jérémy Gottlieb, Audrey
Lasek, Hélène Aubert, Catherine Droitcourt, et al.

82 children (mean age: 9.1 years; females: 61.0%) received 106 treatments. The drugs administered were adalimumab (n=49), etanercept (n=37), ustekinumab (n=15), anakinra (n=2), infliximab (n=2), and secukinumab (n=1).

Five biological drugs are now licensed for use in children: two anti-tumour necrosis factor (TNF) alpha agents (adalimumab and etanercept), an anti-interleukin 12-23 agent (ustekinumab), and two anti-interleukin 17 agents (secukinumab and ixekizumab). These agents are licensed for use in children aged 6 years or above, except for adalimumab, which can be used from the age of 4 years. However, prior to 2020, only the two anti-TNF alpha agents were authorized for use in children under 12 years.

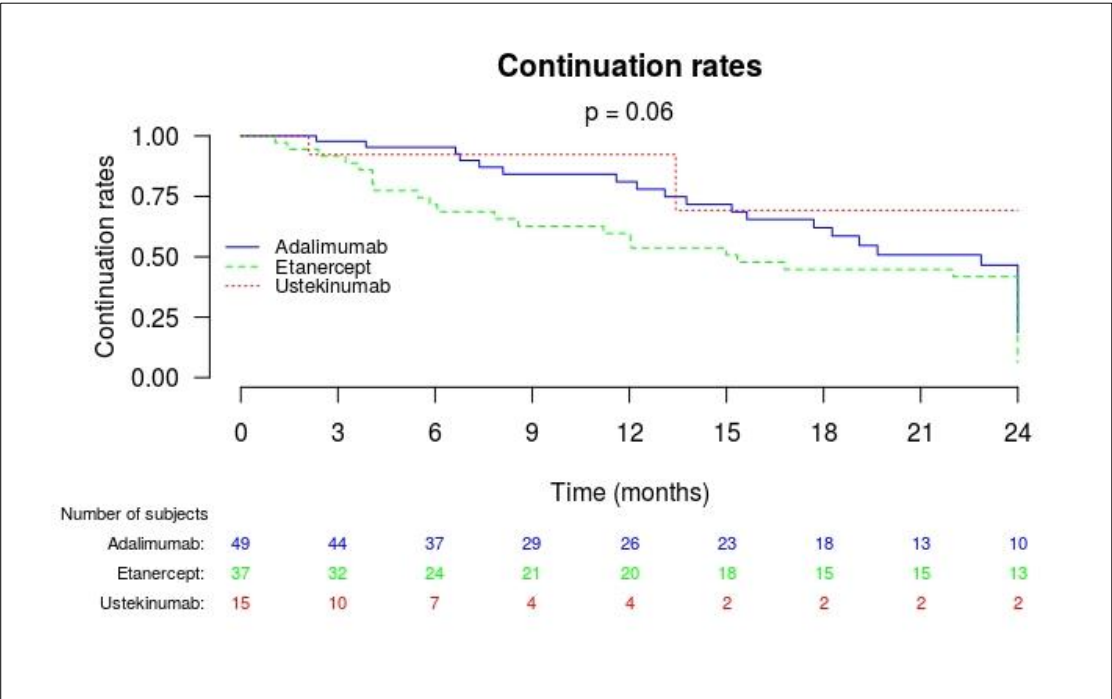
Efficacia delle terapie

Severity assessment	Adalimumab (n=37)		Etanercept (n=33)		Ustekinumab (n=10)		<i>p-values</i> ^a
	Baseline	M3	Baseline	M3	Baseline	M3	
PGA							
Mean ± SD	3.8 ± 0.8 ⁷	1.2 ± 1.1 ¹²	3.7 ± 0.9 ¹³	2.2 ± 1.3 ¹⁷	3.6 ± 0.9 ¹	1.8 ± 1.3 ²	ADA: < 0.0001; ETC: 0.0005; UST: 0.006
PGA=0-1, n (%)	0 (0) ⁷	18 (72.0) ¹²	1 (5.0) ¹³	5 (31.2) ¹⁷	0 (0) ¹	3 (37.5) ²	M3: 0.02
PASI							
Mean ± SD [*]	14.1 ± 9.4 ¹⁵	4.1 ± 11.3 ¹⁸	14.9 ± 9.3 ¹⁶	5.1 ± 4.0 ²⁴	11.6 ± 8.3 ⁰	2.6 ± 2.2 ¹	ADA: 0.001; ETC: 0.002; UST: 0.007
PASI 50, n (%)	-	13 (76.5) ²⁰	-	5 (62.5) ²⁵	-	7 (77.8) ¹	NS
PASI 75, n (%)	-	11 (64.7) ²⁰	-	3 (37.5) ²⁵	-	4 (44.4) ¹	NS
PASI 90, n (%)	-	6 (35.3) ²⁰	-	0 (0) ²⁵	-	1 (11.1) ¹	NS

ADA: adalimumab; ETC: etanercept; UST: ustekinumab; PGA: physician global assessment; PASI: Psoriasis Area Severity Index; PASI 50/75/90: reduction of 50%/75%/90% or more in PASI scores between baseline and M3; M3: evaluation after 3 (± 1) months of treatment. NS: not significant. Superscript: missing data (including all psoriasis phenotypes).

^a Comparisons between means were performed for PGA and PASI scores between baseline and M3. Comparisons of frequencies (%) were performed between adalimumab, etanercept and ustekinumab.

Sicurezza e durata delle terapia



Biotherapy	Adverse event	Causative link	Discontinuation of	
			treatment	Outcome
Adalimumab	Severe urticaria	Probable	Yes	Favourable
Adalimumab ^a	Flu, hospitalized	Probable	No	Favourable
Adalimumab ^a	Body weight gain + 15kg in 6 months	Probable	Yes	No body weight loss after discontinuation
Adalimumab	Acute renal failure	Unlikely	Yes	Favourable
Etanercept	Parotiditis	Probable	No	Favourable
Etanercept	Recurrent infections	Probable	Yes	Favourable
Anakinra	Staphylococcus aureus bacteraemia	Probable	No	Favourable



- 15 anni

- Precedente TP: CsA, UVBTL01 (peggiolata)





12° settimana di TP con adalimumab

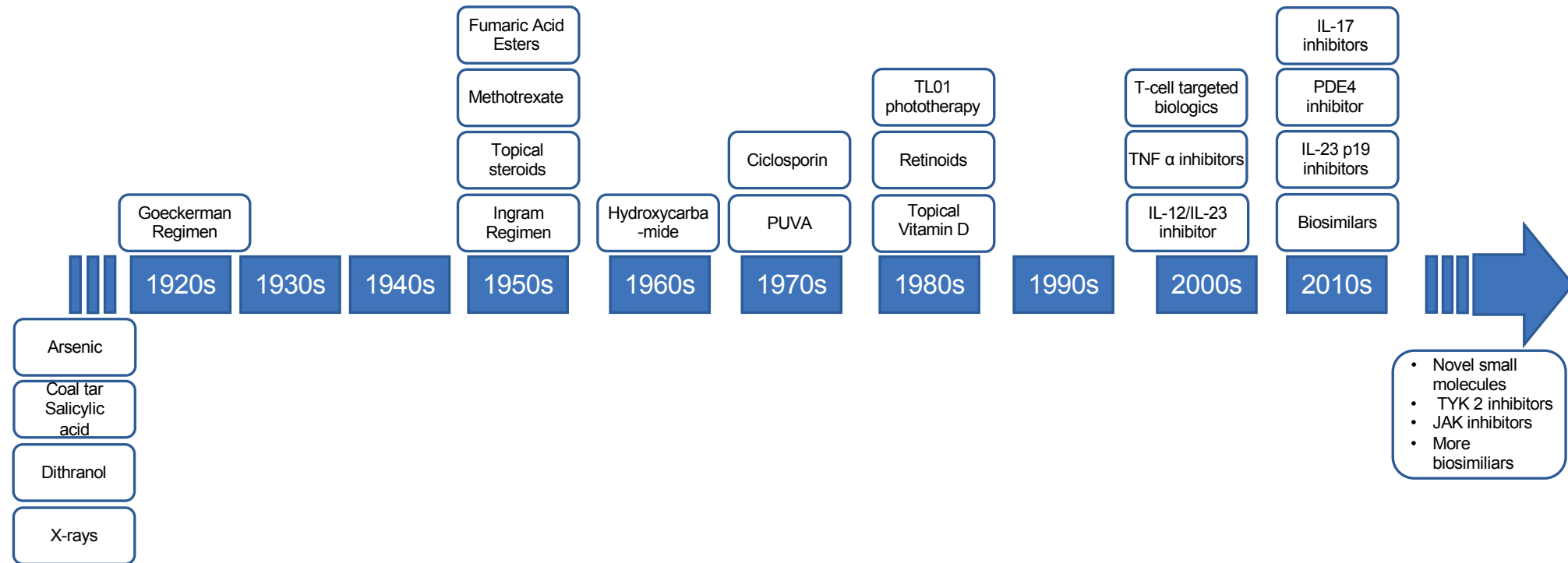




18 mesi di TP con adalimumab

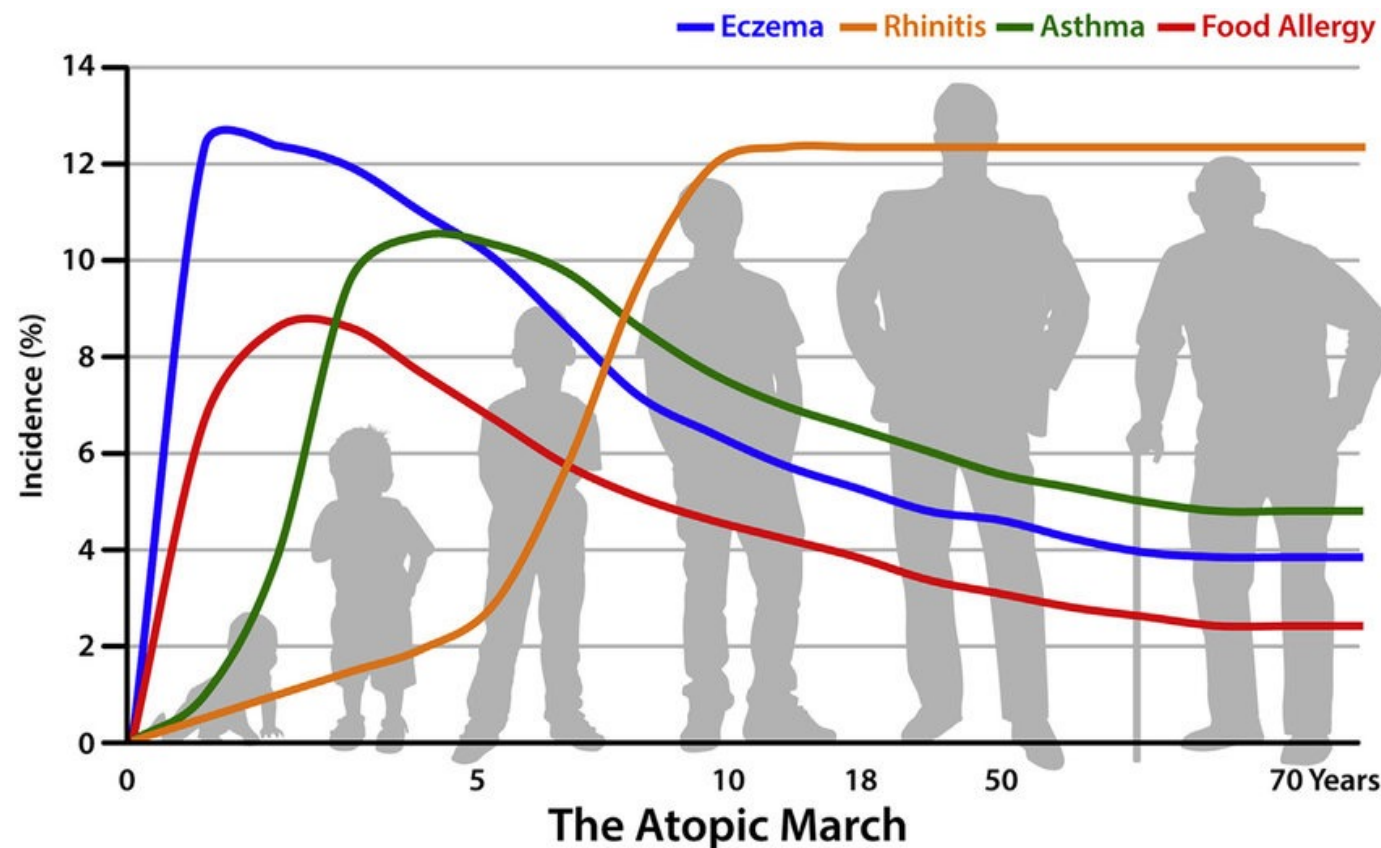


Psoriasi e terapie : passato, presente e futuro



Dermatite atopica

La DA ha una prevalenza del 2-5% nella popolazione generale e fino al 10-20% nei bambini. L'incidenza è massima nei primi anni di vita: il 60% dei pazienti presenta le prime manifestazioni nei primi 2 anni di vita e l'85% nei primi 5 anni di vita.





Narrative review on the management of moderate-severe atopic dermatitis in pediatric age of the Italian Society of Pediatric Allergology and Immunology (SIAIP), of the Italian Society of Pediatric Dermatology (SIDerP) and of the Italian Society of Pediatrics (SIP)

Elena Galli¹, Anna Belloni Fortina², Giampaolo Ricci³, Nunzia Maiello⁴, Iria Neri⁵, Ermanno Baldo⁶, Irene Berti⁷, Domenico Bonamonte⁸, Lucetta Capra⁹, Elena Carboni¹⁰, Rossella Carello¹, Francesca Caroppo², Giovanni Cavagni¹¹, Iolanda Chinellato¹², Francesca Cipriani¹³, Pasquale Comberiati¹⁴, Andrea Diociaiuti¹⁵, Vito Di Lernia¹⁶, Marzia Duse¹⁷, Cesare Filippeschi¹⁸, Arianna Giannetti^{19*}, Mattia Giovannini²⁰, Amelia Licari²¹, Gian Luigi Marseglia²², Manuela Pace²³, Annalisa Patrizi^{5,24}, Giovanni Battista Pajno²⁵, Diego Peroni¹⁴, Alberto Villani²⁶ and Lawrence Eichenfield²⁷

Tacrolimus ointment

- children aged <2 years
- 0.03%: 2- <16 years;
- 0.1%: ≥ 16 years.
- The use in this age group is off-label, but with various studies supporting the safety of use at age <2 years.

Ciclosporina A e Dermatite Atopica

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MTX e DA

MTX appears to have a slow response (8-12 weeks) but is maintained over the long term. The recommended therapeutic dose in children is between 0.2 and 0.5 mg/ kg/week (maximum 25 mg/week) and the duration of treatment is 10–16 weeks. The drug can be increased by 2.5–5 mg/week and decreased by 2.5 mg/week, up to the lowest effective dose.

In conclusion, the off-label use of MTX can be considered as a second-line systemic treatment option, in particular when prolonged treatment is needed.

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Wollenberg A, Christen-Zäch S, Taieb A, Paul C, Thyssen JP, de Bruin- Weller M. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. J Eur Acad Dermatol Venereol. 2020;34:2717–44.

Fototerapia e DA

Phototherapy is indicated as a second-choice therapy for moderate and/or relapsing forms of AD not responsive to TCSs and/or TCIs. This treatment, used in both adults and children (typically > 12 years of age), induces improvement in skin lesions, pruritus, and sleep (Strength of recommendation B and level II of evidence).



Wollenberg A, Christen-Zäch S, Taieb A, Paul C, Thyssen JP, de Bruin- Weller M. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. J Eur Acad Dermatol Venereol. 2020;34:2717–44.

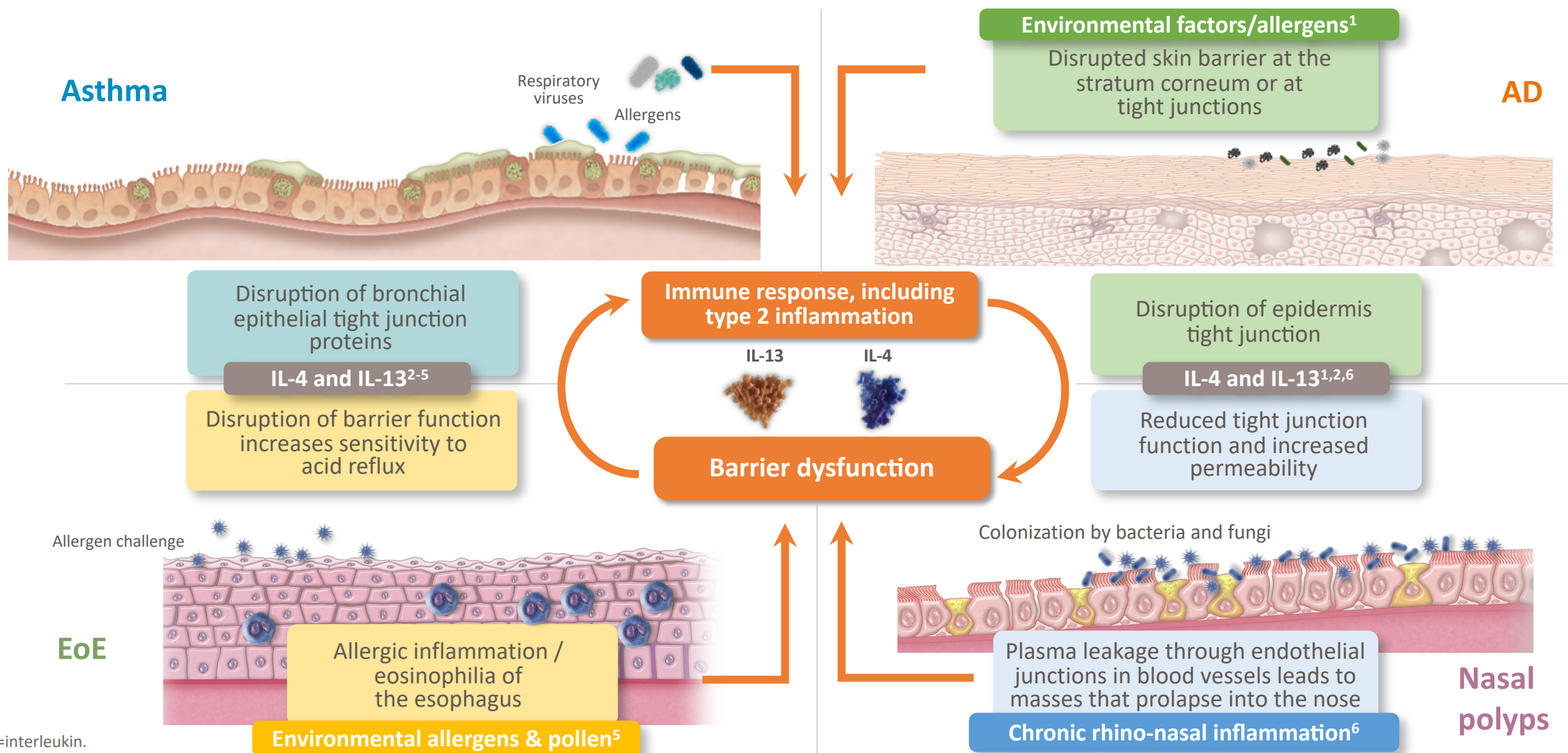
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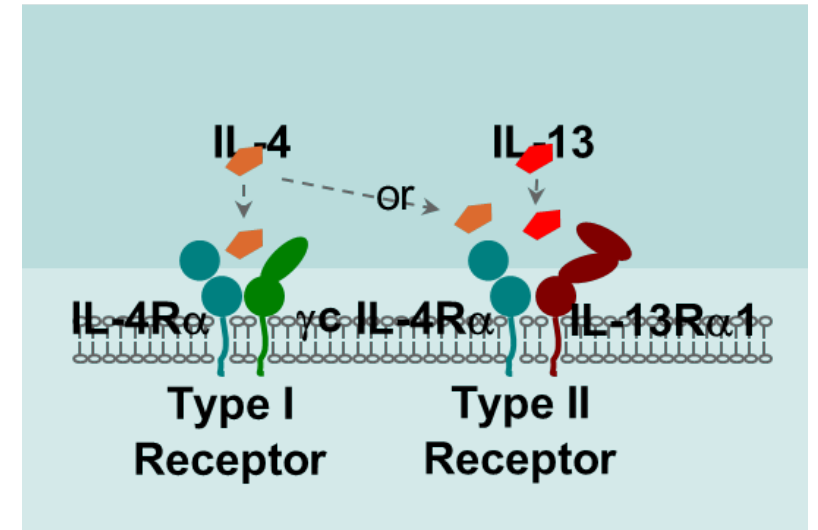
Barrier Disruption is Common Across Multiple Type 2 Inflammatory Diseases with Underlying Type 2 Inflammation



1. Weidinger S, et al. *Nat Rev Dis Primers*. 2018;4(1):1. 2. Schleimer RP, Berdinokivs S. *J Allergy Clin Immunol*. 2017;139:1752-1761. 3. Saatian B, et al. *Tissue Barriers*. 2013;1(2):e24333. 4. Sugita K, et al. *J Allergy Clin Immunol*. 2018;141(1):300-310. 5. Lambert KA, et al. *J Transl Genet Genom*. 2018;2:11. 6. Stevens WW, et al. *J Allergy Clin Immunol*. 2015;136(6):1442-1453.

Terapia: Dupilimab

Un anticorpo monoclonale interamente **umano** che agisce contro il recettore alfa dell'interleuchina (IL)-4 provocando la **doppia inibizione**: inibisce la trasmissione sia del segnale **di IL-4 che IL-13**



Dupilumab: innovatività EMA e AIFA

Versione 1.0_CTS aprile 2021

VALUTAZIONE DELL'INNOVATIVITA'

Medicinale: Dupixent® (dupilumab)

Indicazione autorizzata EMA: Dupixent® è indicato per il trattamento della dermatite atopica grave nei bambini di età compresa tra 6 e 11 anni eleggibili per la terapia sistemica.

La presente valutazione dell'innovatività si riferisce all'indicazione pediatrica: pazienti adolescenti di età pari o superiore ai 6 anni (< 12 anni) con dermatite atopica (DA) grave eleggibili alla terapia sistemica per risposta inadeguata (*non responder*: malattia non adeguatamente controllata) o intolleranza/controindicazione alle terapie topiche. In particolare l'indicazione per la quale è stata richiesto il riconoscimento dell'innovatività è l'indicazione proposta per l'ammissione alla rimborsabilità, come di seguito riportato.

Indicazione oggetto di richiesta di riconoscimento dell'innovatività:

Pazienti adolescenti di età compresa tra i 6 e 11 anni con dermatite atopica grave eleggibili per la terapia sistemica, che presentano:

- EASI $\geq$ 24

oppure una delle seguenti caratteristiche:

1. Localizzazione in zone visibili e/o sensibili quali: viso/collo e/o mani e/o genitali;
2. Valutazione del prurito con scala NRS $\geq$ 7;
3. Valutazione della qualità della vita con indice CDLQI $\geq$ 10.

BISOGNO TERAPEUTICO		
MASSIMO	Assenza di opzioni terapeutiche per la specifica indicazione.	O
IMPORTANTE	Presenza di alternative terapeutiche per la specifica indicazione, ma che non producono impatto su esiti clinicamente rilevanti e validati per la patologia in oggetto.	×
MODERATO	Presenza di alternative terapeutiche per la specifica indicazione con impatto valutabile come limitato su esiti riconosciuti come clinicamente rilevanti e/o con un profilo di sicurezza incerto o non del tutto soddisfacente.	O
SCARSO	Presenza di una o più alternative terapeutiche per la specifica indicazione con impatto valutabile come elevato su esiti riconosciuti come clinicamente rilevanti e con un profilo di sicurezza favorevole.	O
ASSENTE	Presenza di alternative terapeutiche per la specifica indicazione in grado di modificare la storia naturale della malattia e con un profilo di sicurezza favorevole.	O

Commento: lo spettro di alternative terapeutiche utilizzate comunemente nella pratica clinica per il trattamento della dermatite atopica (DA) pediatrica nel setting d'interesse (**pazienti pediatrici di età $\geq$ 6 e < 12 anni con DA grave eleggibili per la terapia sistemica**, con risposta inadeguata/intolleranza/controindicazione al trattamento con le terapie topiche disponibili, quali corticosteroidi e inibitori della calcineurina per uso topico [TCS o TCI]), comprende la terapia farmacologica con i corticosteroidi (CS) e gli immunosoppressori non steroidei sistemici e la fototerapia con raggi UVB a banda stretta (nbUVB) o con raggi UVA1. Quest'ultima rappresenta un'opzione alternativa alla terapia sistemica, sebbene l'utilizzo a lungo termine (> 4 mesi per ciclo) sia sconsigliato dalle principali Linee Guida per il potenziale rischio cancerogeno cutaneo, tuttavia non supportato da evidenze in letteratura, in via cautelativa. Le terapie farmacologiche sistemiche ad oggi disponibili che si posizionano in alternativa a Dupixent nella stessa linea di trattamento per le forme severe di DA nei bambini di età 6-11 anni, presentano anche importanti limitazioni: un elevato rischio di effetti avversi che non consentono l'attuazione di una terapia a lungo termine come la patologia cronicorecidivante richiede; un'efficacia limitata solo nel controllare i sintomi, trattare in fase acuta o prevenire le riacutizzazioni, ma non in grado di fornire un controllo prolungato adeguato dei segni e sintomi della malattia; dati da studi clinici randomizzati e controllati limitati a supporto del profilo di efficacia e sicurezza e del loro uso nella pratica clinica. In particolare **i CS sistemici sono indicati per il trattamento a breve termine, in fase acuta e in casi selezionati, di severe esacerbazioni**. La terapia a lungo termine non è raccomandata nei pazienti pediatrici e negli adolescenti, in considerazione della delicata fase di crescita in cui si trovano i pazienti in questa fascia di età, per i potenziali effetti avversi associati all'utilizzo cronico, tra cui la soppressione dell'asse ipotalamo- ipofisi-surrene, l'interferenza con lo sviluppo puberale e strutturale, la sindrome di Cushing, il ritardo nella crescita, l'obesità, l'iperglicemia, l'ipertricosi, nonché per evitare il rischio di un effetto rebound che consegue l'interruzione del trattamento con severe riacutizzazioni della malattia. **Altre terapie immunosoppressive sistemiche, come la ciclosporina (CsA), il metotrexato (MTX), l'azatioprina (AZA) e il micofenolato mofetile (MMF) sono utilizzate off-label.**

History of approvals of dupilumab for atopic dermatitis by international regulatory agencies

Approval date	FDA	EMA	AIFA
Adults with moderate to severe AD inadequately controlled	March 2017	September 2017	August 2018 ^a
Adolescents 12-17 years, with moderate to severe AD inadequately controlled	March 2019	August 2019	November 2020 ^b
Children 6-11 years, with moderate to severe AD inadequately controlled	May 2020	October 2020	January 2022 ^c

^a Adult patients with EASI score ≥ 24 , for whom cyclosporine therapy is contraindicated, ineffective, or not tolerated. Reimbursement class: H, medicinal product subject to restrictive medical prescription, to be renewed from time to time, sold to the public on prescription from hospitals or dermatologist specialists (RNRL)

^b Adolescents eligible for systemic therapy without prior use of cyclosporine; medicine subject to a limited medical prescription, to be renewed from time to time, sold to the public on prescription from hospitals or specialists - dermatologist, pulmonologist, allergist, otolaryngologist, immunologist and pediatrician (RNRL)

^c From 20 December 2022 it is possible to use dupilumab in a reimbursable regime as an innovative non-oncological drug for the treatment of severe AD in children aged 6 to 11 eligible for systemic therapy who have an EASI score ≥ 24 or one of the following characteristics: localization in visible and / or sensitive areas; evaluation of pruritus with NRS ≥ 7 scale; quality of life assessment with CDLQI index ≥ 10

Recommended dose of dupulumab for the treatment of pediatric atopic dermatitis

Adolescents between the ages of 12 and 17		
<i>Bodyweight</i>	<i>Starting dose</i>	<i>Subsequent doses</i>
Less than 60 kg	400 mg (two 200 mg injections)	200 mg every 2 weeks
60 kg or more	600 mg (two 300 mg injections)	300 mg every 2 weeks
Children between the ages of 6 and 11		
<i>Bodyweight</i>	<i>Starting dose</i>	<i>Subsequent doses</i>
15 to less than 60 kg	300 mg (one 300 mg injection) on day 1, followed by 300 mg on day 15	300 mg every 4 weeks ^a , starting 4 weeks after the day 15 dose
60 kg or more	600 mg (two 300 mg injections)	300 mg every 2 weeks

^a The dose may be increased to 200 mg every 2 weeks in patients weighing 15 kg to less than 60 kg based on the physician's assessment

GUIDELINES

Diagnosis and management of moderate to severe atopic dermatitis in adolescents.

A Consensus by the Italian Society of Dermatology and Venereology (SIDeMaST), the Italian Association of Hospital Dermatologists and Public Health (ADOI), the Italian Association of Hospital and Territorial Allergists and Immunologists (AAIITO), the Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC), the Italian Society of Pediatric Allergy and Immunology (SIAIP), the Italian Society of Allergological, Occupational and Environmental Dermatology (SIDAPA), and the Italian Society of Pediatric Dermatology (SIDerP)

Piergiacomo CALZAVARA-PINTON ¹ *, Anna BELLONI FORTINA ², Domenico BONAMONTE ³, Gian L. MARSEGLIA ⁴, Michele MIRAGLIA DEL GIUDICE ⁵, Antonino MUSARRA ⁶, Eustachio NETTIS ⁷, Iria NERI ⁸, Cataldo PATRUNO ⁹, Luca STINGENI ¹⁰, Ketty PERIS ¹¹ on behalf of RADAR Group ‡

Dupilumab is approved for adolescents with moderate to severe AD eligible for systemic therapy. Based on the experience acquired in adult patients and considering its proven efficacy and high safety profile, dupilumab can currently be considered in adolescents as a **first-choice systemic treatment**.



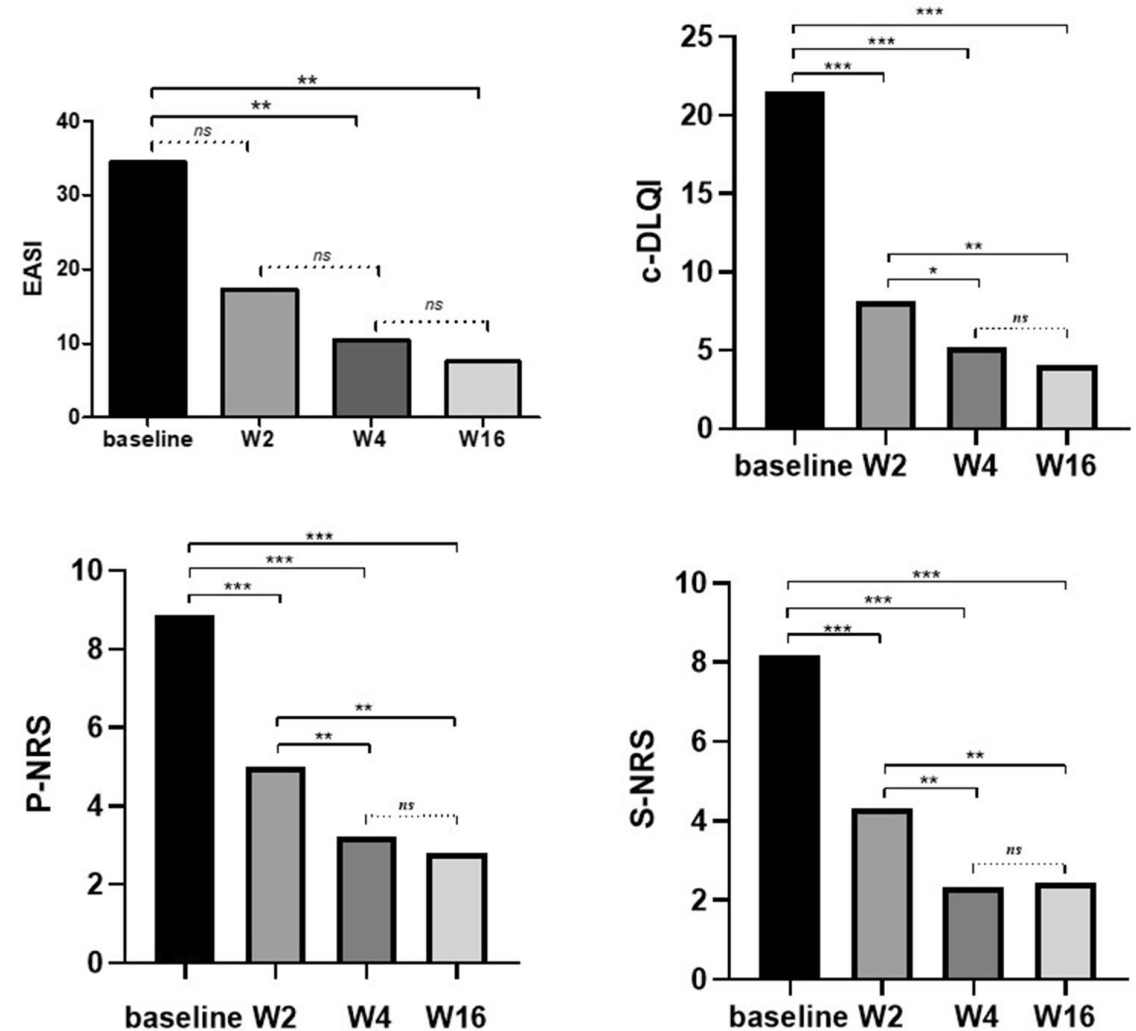
Dupilumab Treatment in Children Aged 6–11 Years With Atopic Dermatitis: A Multicentre, Real-Life Study

Maddalena Napolitano¹ · Gabriella Fabbrocini² · Iria Neri³ · Luca Stingeni⁴ · Valeria Boccaletti⁵ · Vincenzo Piccolo⁶ · Giuseppe Fabrizio Amoroso⁷ · Giovanna Malara⁸ · Rocco De Pasquale⁹ · Eugenia Veronica Di Brizzi⁶ · Laura Diluvio¹⁰ · Luca Bianchi¹⁰ · Andrea Chiricozzi^{11,12} · Adriana Di Guida² · Elisabetta Del Duca¹³ · Viviana Moschese¹³ · Vito Di Lernia¹⁴ · Federica Dragoni¹⁵ · Michaela Gruber¹⁶ · Katharina Hansel⁴ · Amelia Licari¹⁷ · Sara Manti¹⁸ · Salvatore Leonardi¹⁸ · Luca Mastorino¹⁹ · Michela Ortoncelli¹⁹ · Eugenio Provenzano⁷ · Antonino Palermo²⁰ · Vincenzo Patella²¹ · Tiziana Peduto²¹ · Elena Pezzolo²² · Viviana Piras²³ · Luca Potestio² · Teresa Battista² · Rosanna Satta²⁴ · Stefania Termine²⁵ · Paolo Palma²⁶ · Paola Zangari²⁶ · Cataldo Patruno²⁷

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A total of 55 AD children (24 males [43.64%], 31 females [56.36%]; mean age 9.35 ± 1.75 years) were included. A significant improvement in EASI score, P-NRS, S-NRS and c-DLQI was observed from baseline to W16 of treatment with dupilumab. In particular, at W16 the proportion of patients achieving **EASI75 was 74.54%**. Moreover, at the same timepoint a significant mean percentage reduction for P-NRS, S-NRS and c-DLQI was also observed (68.39%, 70.22% and 79.03%, respectively).

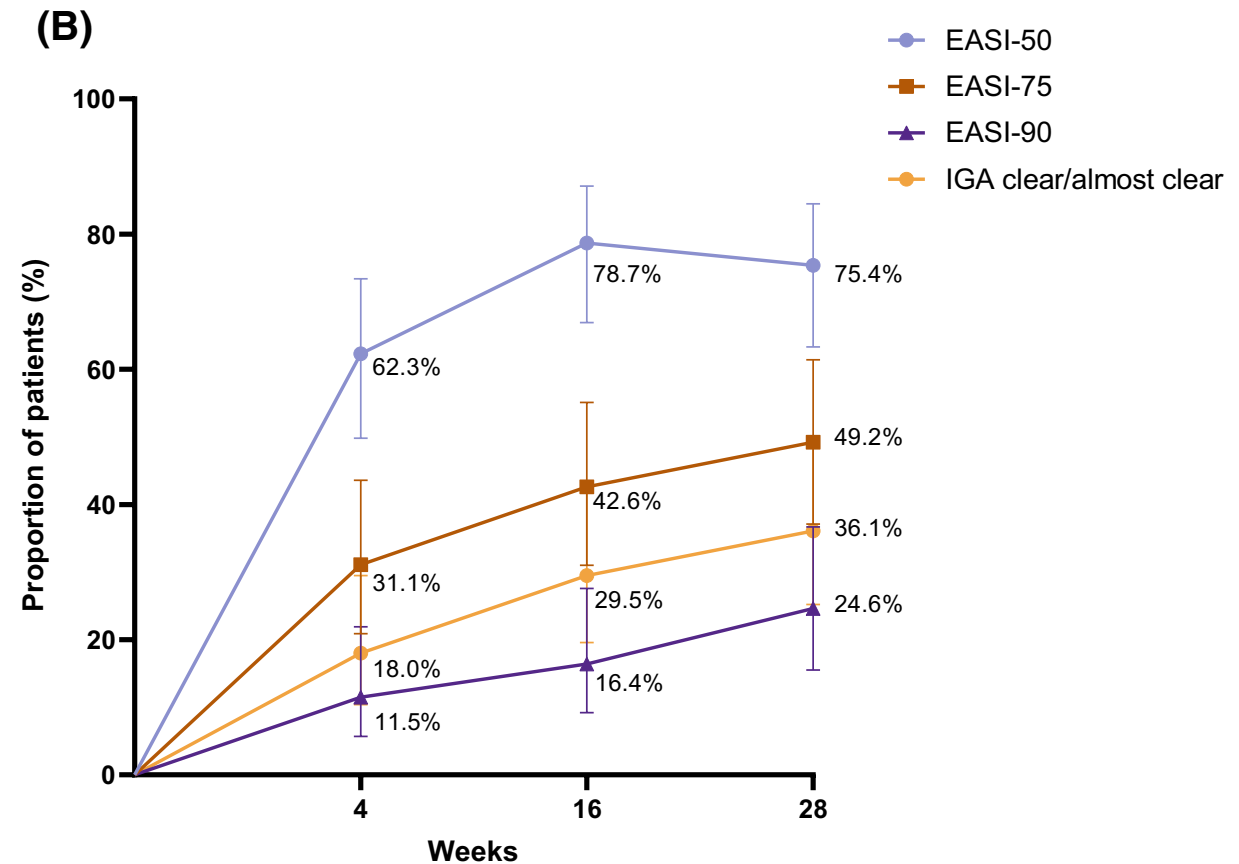


Mean values of EASI, P-NRS, S-NRS and c-DLQI pre- and post-dupilumab treatment in children with atopic dermatitis aged from 6 to 11 years. Mean values of EASI (Eczema Area and Severity Index), S-NRS (Sleep Numerical Rating Scale), P-NRS (Pruritus Numerical Rating Scale) and c-DLQI (Children's Dermatology Life Quality Index) for the study population at baseline and after week 2 (W2), W4 and W16 of dupilumab treatment. Statistical significance was assessed by The Mann–Whitney test and Fisher test: ***p < 0.0001, **p < 0.001, *p < 0.005; ns not significant

Dupilumab in daily practice for the treatment of pediatric atopic dermatitis: 28-week clinical and biomarker results from the BioDay registry

Esmé Kamphuis¹ | Celeste M. Boesjes² | Laura Loman¹ | Daphne S. Bakker² |
Mila Poelhekkens¹ | Nicolaas P. A. Zuithoff³ | Marijke Kamsteeg⁴ |
Geertruida L. E. Romeijn¹ | Femke van Wijk⁵ | Marjolein S. de Bruin-Weller² |
Marlies de Graaf² | Marie L. A. Schuttelaar¹

Sixty-one patients were included. Respectively 75.4%, 49.2%, and 24.6% reached EASI-50, EASI-75, and EASI-90 and 36.1% achieved an IGA-score (almost) clear. Improvement of ≥ 4 points on POEM, NRS-pruritus, and NRS-pain was reached by 84.7%, 45.3%, and 77.4%, respectively. Most reported side effects were conjunctivitis (n = 10) and headache (n = 4).



Orticaria Cronica Spontanea (CSU)

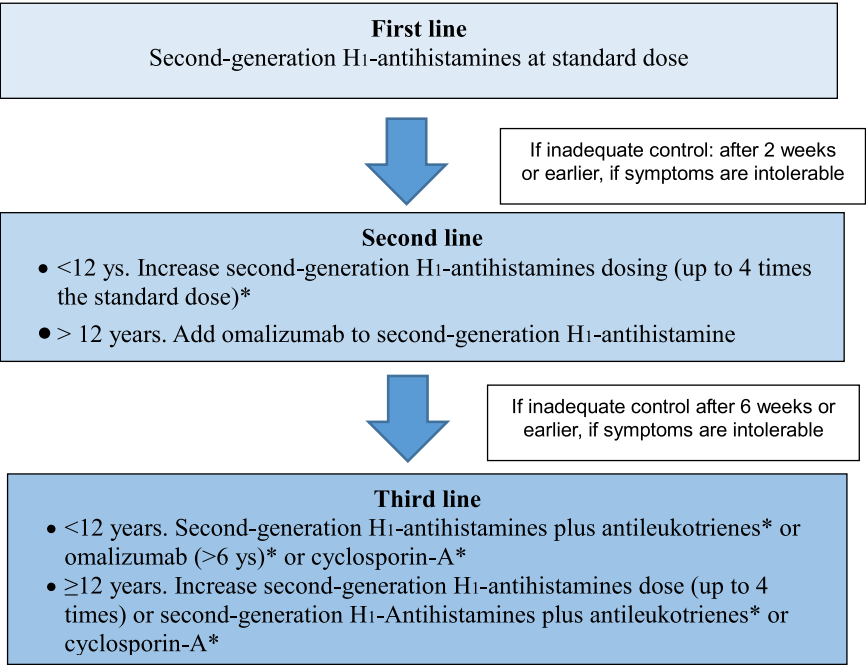
- Presenza quotidiana (o con brevi intervalli liberi legati alla terapia) di pomfi migranti, pruriginosi, associati o meno ad angioedema (AE), per un periodo di tempo di almeno 6 settimane.
- Ha una frequenza nel bambino uguale o perfino superiore a quella dell'adulto, con una prevalenza in aumento (1% della popolazione generale).
- In età pediatrica non sembrano esistere differenze significative tra maschi e femmine.
- Studi clinici sia prospettici che retrospettivi su popolazioni pediatriche rappresentative hanno descritto una probabilità di remissione della CSU a un anno dall'esordio tra il 10 e il 32% e a 5 anni dal 38 al 72%

REVIEW Open Access

Management of chronic urticaria in children: a clinical guideline



Carlo Caffarelli^{1†}, Francesco Paravati^{2†}, Maya El Hachem³, Marzia Duse⁴, Marcello Bergamini⁵, Giovanni Simeone⁶, Massimo Barbagallo⁷, Roberto Bernardini⁸, Paolo Bottau⁹, Filomena Bugliaro¹⁰, Silvia Caimmi¹¹, Fernanda Chiera², Giuseppe Crisafulli¹², Cristiana De Ranieri¹³, Dora Di Mauro¹⁴, Andrea Diociaiuti³, Fabrizio Franceschini¹⁵, Massimo Gola¹⁶, Amelia Licari¹¹, Lucia Liotti¹⁷, Carla Mastroiilli¹⁸, Domenico Minasi¹⁹, Francesca Mori²⁰, Iria Neri²¹, Aurelia Pantaleo²², Francesca Saretta^{23,24}, Carlo Filippo Tesi¹⁰, Giovanni Corsello²⁵, Gian Luigi Marseglia¹¹, Alberto Villani²⁶ and Fabio Cardinale^{18*}



Second-generation H ₁ -antihistamines	Pharmaceutical form	Age and/or weight	Dose
Cetirizine	Drops 10 mg/ml (1 drop = 0,5 mg)	2–6 years	2.5 mg b.i.d.
	Oral solution 1 mg/ml	6–12 years	5 mg b.i.d.
	Tablets 10 mg	12–18 years	10 mg q.d.
Loratadine	Syrup 1 mg/ml Tablets 10 mg	2–12 years (< 30 kg)	5 mg q.d.
		2–12 years (> 30 kg)	10 mg q.d.
		12–18 years	10 mg q.d.
Fexofenadine	Tablets 120 mg Tablets 180 mg (Tablets/syrup 30 mg in US/UK)	12–18 years	120–180 mg q.d.
		(US> 2 years, UK > 6 years)	30 mg q.d.
Levocetirizine	Drops 5 mg/ml (1 drop = 0,25 mg) Tablets 5 mg	2–6 years (in US > 6 months)	1.25 mg q.d.
		> 6 years	5 mg q.d.
Desloratadine	Oral solution 0,5 mg/ml Tablets 2.5 mg Tablets 5 mg	1–5 years	1.25 mg q.d.
		6–11 years	2.5 mg q.d.
		> 12 years	5 mg q.d.
Acrivastine	Syrup 8 mg/10 ml Tablets 8 mg	> 12 years	8 mg t.i.d.
Rupatadine	Oral solution 1 mg/ml Tablets 10 mg	2–11 years (< 25 kg)	2.5 mg q.d.
		2–11 years (> 25 Kg)	5 mg q.d.
		> 12 years old	10 mg q.d.
Bilastine	Syrup 2.5 mg/ml Tablets 10 mg Tablets 20 mg	> 6 years (> 20 kg)	10 mg q.d.
		> 12 years	20 mg q.d.
		> 12 years (> 2 aa in Europe)	10–20 mg q.d. (0.2 mg/kg q.d.)
Ebastine	Tablets 10 mg Tablets 20 mg (Syrup 5 mg/ml)	> 12 years (> 2 aa in Europe)	10–20 mg q.d. (0.2 mg/kg q.d.)



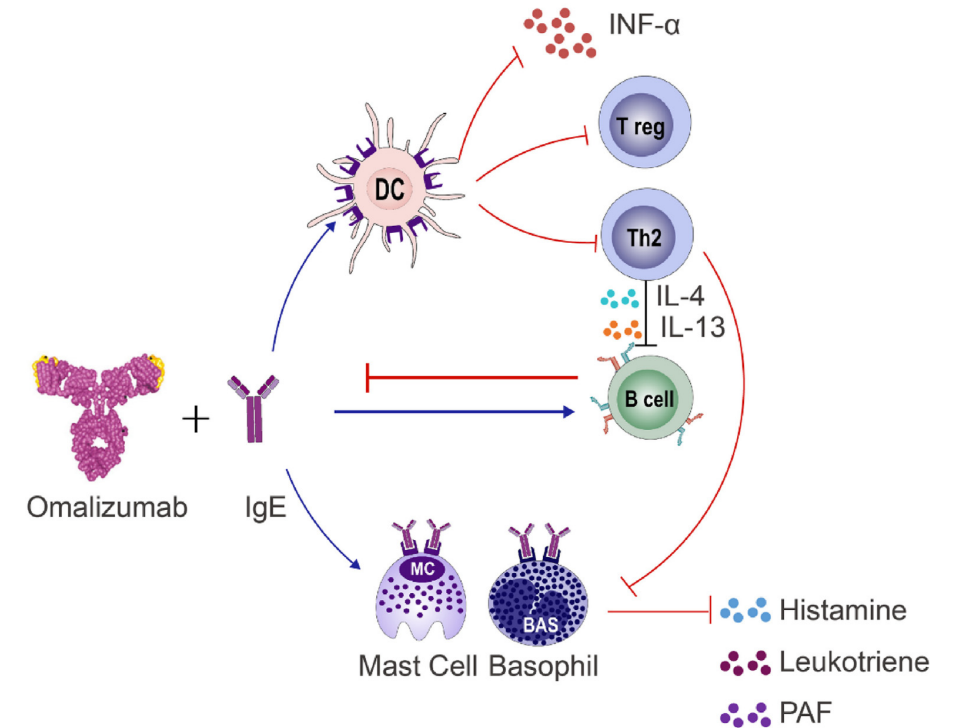
Pediatric usage of Omalizumab: A promising one

Lin Yu, MD^a, Huishan Zhang, MD^{b,c}, Jianwei Pan, MD^a and Leping Ye, MD, PhD^{b*}

ABSTRACT

Allergic and related diseases have a substantial epidemiological impact on the pediatric population. Small molecule-based medicines have been traditionally used to manage the diseases. Omalizumab is the first monoclonal antibody-based medicine used in children's allergy and shows great promises. It binds to free IgE and prevents it from binding to IgE receptors, thus interrupting the IgE-dependent allergic inflammatory cascade. Vast amounts of data demonstrate its effectiveness and well tolerance by patients, including the children. However, the drug was only approved to use in allergic asthma and chronic spontaneous urticaria (CSU), though other applications were explored in clinical trials. In this review, we summarized current pediatric applications of omalizumab in allergic diseases, focusing on its usages beyond asthma and CSU, including allergic rhinitis, allergic bronchopulmonary aspergillosis, vernal keratoconjunctivitis, food allergy and atopic dermatitis. In addition, we highlighted the unmet needs and controversial issues of anti-IgE therapy.

Keywords: Allergy treatment, IgE, Pediatrics, Omalizumab



Indicazioni Omalizumab

Xolair è indicato, come terapia aggiuntiva, per il trattamento dell'orticaria cronica spontanea in pazienti adulti e adolescenti (età pari o superiore a **12 anni**) con risposta inadeguata al trattamento con antistaminici H1.

Asma allergico

Xolair è indicato negli adulti, negli adolescenti e nei bambini di età compresa tra **6 e <12 anni**.

Rinosinusite cronica con polipi nasali (CRSwNP)

Xolair è indicato come terapia aggiuntiva ai corticosteroidi intranasali per il trattamento di adulti (età pari o superiore a **18 anni**) con CRSwNP grave per i quali la terapia con i corticosteroidi intranasali non fornisce un controllo adeguato della malattia.



Grazie per
l'attenzione

