AIU 2017 Grindelwald, workshop 9

Drug hypersensitivity: Skin tests, lab or what?

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Model-Case 1

- 41 y ♂, acute sinusitis
- ca. 1 hour after oral intake of amoxicillin-clavulanat: itching rash
- recovery on the same day
- formerly good tolerance of antibiotics
- no re-exposition

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Preliminary assessment: Urticaria in temporal correlation with amoxicillin clavulanate

Causality

other reasons	no other Xenobiotics	-
	Infection	+
	other unknown factor	+
pharmacological side effect		- (?)
hypersensitivity	'unspecific'	- (?)
	IgE-mediate-type-allergy	++

Estimated probability for IgE mediated allergy to amoxicillin clavulanat: ~ 50%

Further investigations:

- Active phase of reaction: Tryptase within 0.5- 4 h
- Tests to identify the culprit drug after the active phase

skin test (prick) i.d.	sensitivity ~ 60% specificity ~ 90%
in vitro tests: IgE, CAST, LTT...)	sensitivity, ~ 60%, specificity ?
provocation-test	sensitivity > 90%, specificity ?

Mayorga et al. Allergy 2016;71: 1103-1134
Romano et al. Allergy 2009;64: 249-253
Brockow et al. Allergy 2013;68: 702–12

Change of probability

skin test (prick) i.d.	sensitivity ~ 60% specificity ~ 90%	neg.: 50% → ~ 20% pos.: 50% → > 95%
in vitro Teste: IgE, CAST, LTT...)	sensitivity ? ~ 60%, specificity ?	neg.: 50% → ? > 20% Pos.: 50% → ?
provocation-test	sensitivity > 90%, specificity ?	Neg.: 50% → < 5% Pos.: 50% → ?

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Risk for severe anaphylaxis (Mueller grading ≥ II; IV)
- re-exposure penicillin

	skin test pos.	skin test neg.
penicillin	~ 50%; ~ 8%	8%; ~1%

Müller UR Insect sting allergy. Stuttgart: Gustav Fischer; 1990.

- Recommendation of further therapy?
- Need for further investigations?

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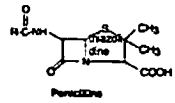
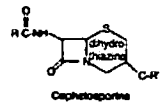
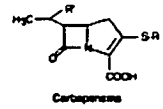
Cross reactivity beta lactams (IgE):



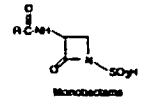
cephalosporins without similar side chain ~ 20%
(avoid cefaclor, cefmandol)



carbapenems: ~ 1%



monobactams: ~ 3% (Ceftazidime)



Romano et al. J Allergy Clin Immunol 2010;126: 994-9

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Risk for severe anaphylaxis (Mueller grading ≥ II; IV)

	skin test pos.	skin test neg.
penicillin	~ 50%; ~ 8%	~8%; < 1%
cephalosporine (without Cefamandol/Cefaclor)	< 10%; < 2%	<1,5%; <0.2%
carbapenem	< 1%; <0.2%	< 0,15%; <0.02%
monobactam	< 1.5%; ~0.2%	< 0,2%; <0.03%

Provocation-test in case of negative skin-test

- Penicillin: 'graded challenge': if relevant co-morbidity with increased need for antibiotic treatment
- alternative betalactam: mostly not compulsory

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Model-Case 2

- 41 y ♂
- 1 hour after oral intake of amoxicillin-clavulanat and metamizol (Novalgin®)
- itching rash
- recovery on the same day
- formerly good tolerance of antibiotics
- no re-exposition

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Preliminary assessment of causality

other reasons:	infection, otherwise healthy		+
pharmacological side effect	metamizole		(+)
	amoxillin-calvulanat		(+)
hypersensitivity	metamizole	'unspecific'	++
		IgE-allergy	++
	amoxicillin-clavulanat	'unspecific'	(+)
		IgE-allergy	++

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Further investigations:

metamizole	**History regarding NSAID intolerance** In case of positive history: Provocation-test regarding threshold/alternative-NSAID?	
	skin test (prick) i.d.:	sens./spec. ~ penicillins
	in vitro tests:	not established

amoxicillin-clavulanat	skin test (prick) i.d.:	cf. model case1
	provocation test	

Cross-reactions:

Sulfonamides

- Sulfadiazine
- Sulfamethoxazole
- Sulfapyridine (Sulfasalazine)
- Sulfaoxazole
- Dapsone

N Engl J Med 2003;349:1628-35

Chinolones

index-reaction	provocation	positive/tested
ciproxin	levofloxacin	1/5 (95% CI 4%- 63%)
ciproxin	mofloxacin	1/3 (95% CI 6%- 79%)
levofloxacin	mofloxacin	3/3 (95% CI44%- 100%)

J Investig Allergol Clin Immunol. 2010;20:607-11

Macrolides

Theoretically low cross-reactivity (different positions of lacton-ring).
Case reports of cross-reactivity (provocation and tests)

International Journal of Immunopathology and Pharmacology 2014; 27:121-6

Cross-reactions:

Vancomycin
Often «Pseudo allergies»;
vasculitic 'rash' between vancomycin und teicoplanin
J Infect 1998;37:82.

Metronidazole
Case reports of cross-reactivity with other Imidazolen
UpToDate® May 2016

Clindamycin
Has not been studied
UpToDate® May 2016

Tetracyclines
Non-IgE-mediated allergic reactions often severe (minocycline); cross-reactivity among has not been studied.
UpToDate® Mai 2016

Aminoglycosides
Predominantly contact dermatitis; high cross-reactivity
UpToDate® Mai 2016

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Cross-reactions:

Anticonvulsants
high cross-reactivity between so called 'aromatic anticonvulsants':
Phenytoin, phenobarbital, primidone, carbamazepine, oxacarabazepine, felbamate, zonisamide lamotrigine.
Alternatives:
1. Benzodiazepines, levetiracetam or gabapentin
2. Topiramat or valproate

Zaccara et al Epilepsia 2007; 48: 1223-44

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Diagnosis of drug allergy for prevention of 1°exposure

- Genetic factors: Genom wide association studies: only MHC
- MHC:
  - B*5701: Abacavir[1] (Flucloxacilline)
  - B*1502: Asian people[2]: Carbamazepine
  - A*3101: Carbamazepine[3]
  - B*5801: Allopurinol[4]
  - HLA-B*57:01: Flucloxacilline DILI[5]

1) NJEM 2008; 358: 568-79
2) Nature 2004;428:486.
3) NJEM 2011, 364: 1134-43
4) Pharmacogenet Genomics 2008: 99-107
5) Nat Genet 2009, 41:816–9.

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Conclusions

- There is no test or procedure which can provide a 100% certain diagnosis
- Don't be fixed only on diagnosis for recommendation of further therapy
- Consider
  - severity of the index-reaction
  - importance of the incriminated drug for the patient
  - availability of alternatives

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Differential diagnosis of AD

Newborns & children

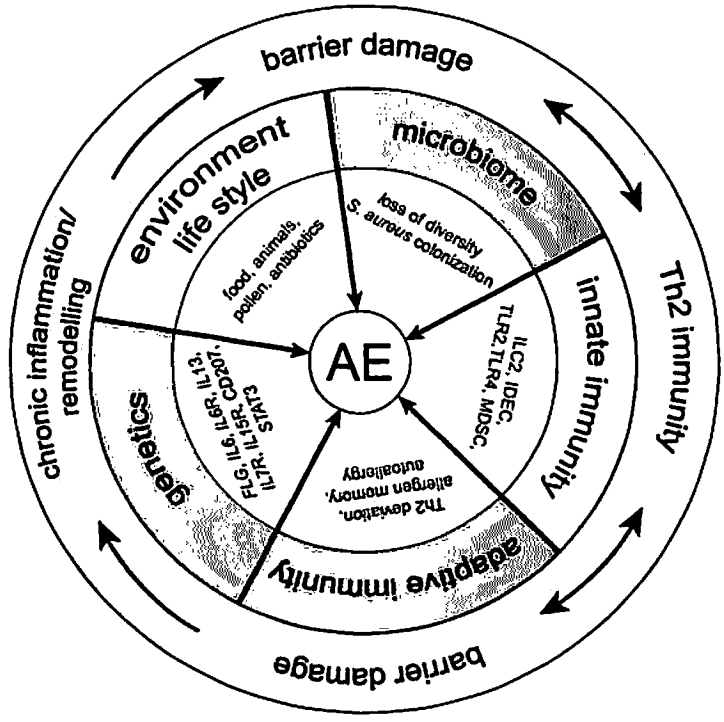
- Seborrheic dermatitis
- Scabies
- Acrodermatitis enteropathica
- Psoriasis
- Prurigo simplex
- Langerhans cell histiozytosis
- Gianotti-Crosti syndrome
- Miliaria rubra
- Hereditary diseases: Ichthyosis vulgaris, Hypohidrotic ektodermal dysplasia, Wiskott-Aldrich syndrome, Hyper-IgE syndrome, Netherton syndrome, Di-George syndrome, Omenn syndrome

Adults

- Toxic & allergic contact dermatitis
- Psoriasis
- Seborrheic dermatitis
- Infections (fungal, viral, scabies, HIV)
- Bullous dermatotsis
- Dermatomyositis, Lupus erythematodes
- CTCL (Mycosis fungoides, Sezary syndrome)
- Acquired ichthyoses
- Prurigo diseases

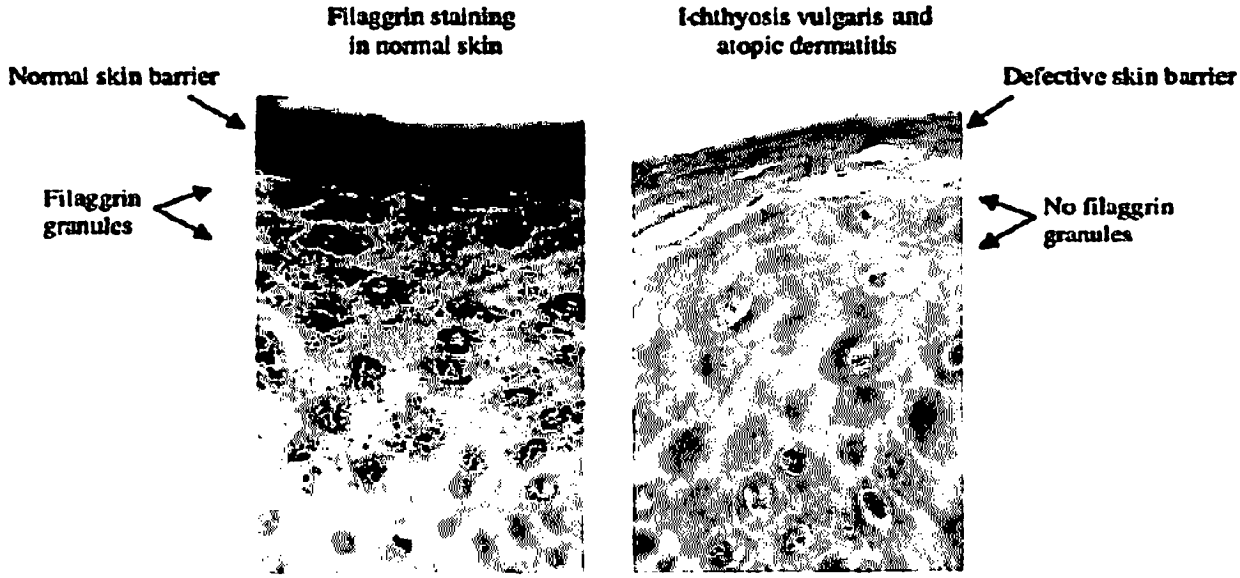
Adapted from Greisser et al. Schweiz Med Forum 2009;9(33):566

Pathogenesis of AD



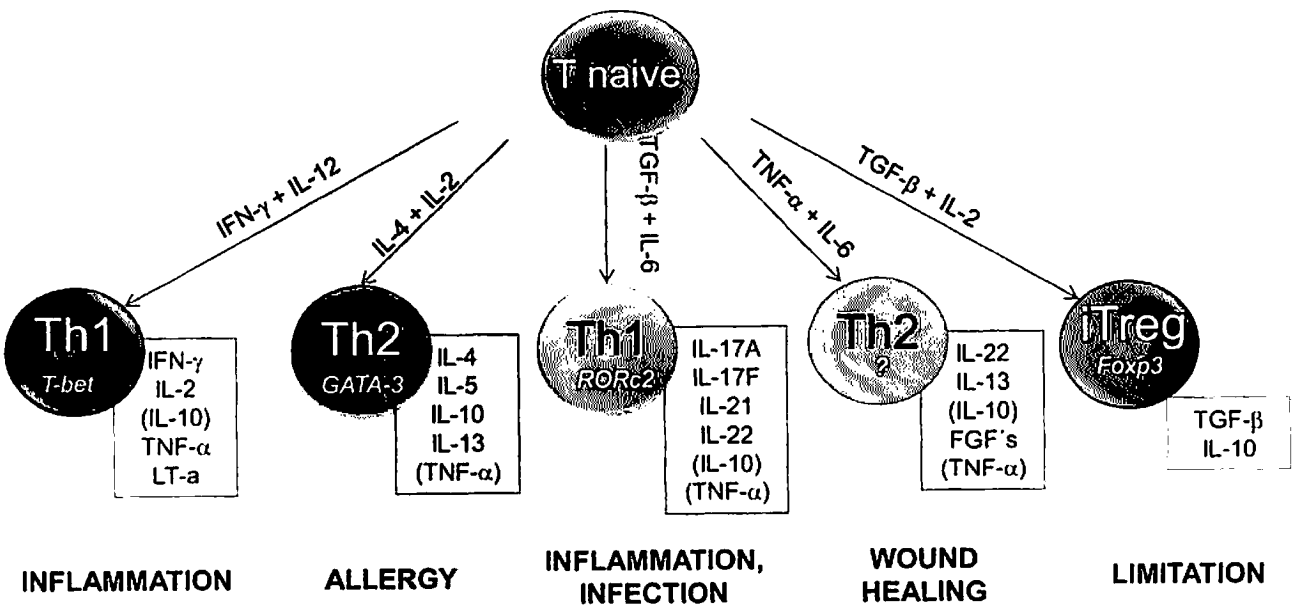
Eyerich K et al, Trends Immunol 2015

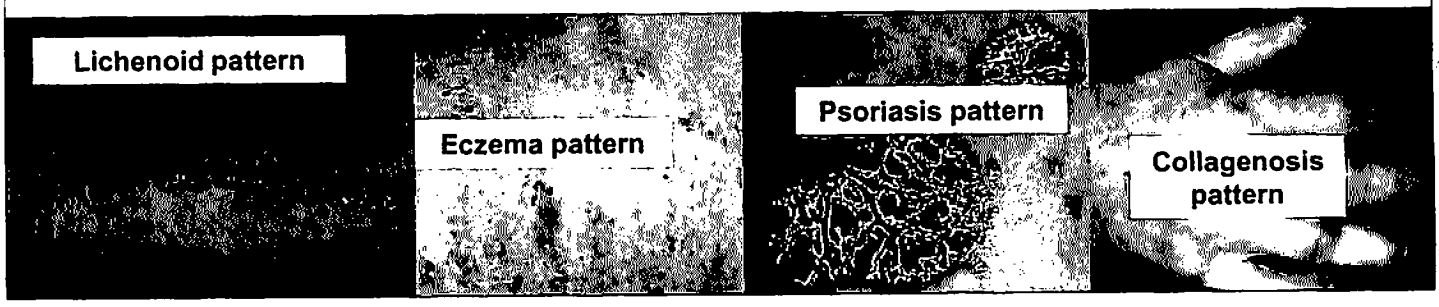
Barrier damage



Irvine et al Nat Genetics 2006
Irvine & Mc Lean JID 2006

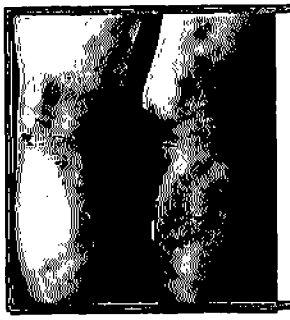
T cells: a complex model





Current adapted treatment of AD

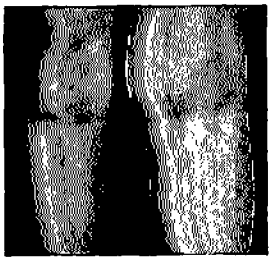
AVOID TRIGGER FACTORS



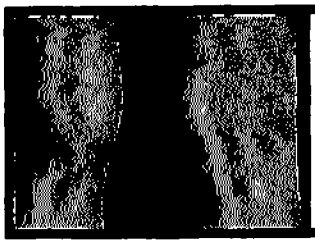
Topical steroids

systemic antibiotics (e.g. Cefuroxim),
systemic antiviral therapy (e.g. Aciclovir i.v.),
systemic immunesuppressivs (e.g. Ciclosporin)

Therapeutic index! Only class 2 and 3 potency
No old combination therapies (e.g. Decoderm tri, Fucicort), use NRF11.145!
Only once daily!
Calcineurin inhibitors (Elidel, Protopic [children 0,03%, adults 0,1%])



Pro-active therapy: Protopic 0,1%, mild seroids (e.g. NRF 11.144 Prednicarbat 0,15% oder 0,25%, with Octenidin NRF 11.145)
UV light therapy (UVA1, less UV-B)
Anti-pruritic: e.g. black tea, Polidocanol (e.g. Optiderm/ Thesit in DAC Basis; Tannosynt bathings)
Antiseptics (e.g. Fucidine, kalium permanganate (cave!), Octenisept, Triclosan 1% in DAC Basis Creme,
coloring (Eosin 1%, Methylrosanilin 1%)



Basic emollients, e.g. Alfason Basis Cresa, Unguentum emulsificans aquosum with/without 5% glycerine, Neuroderm
Urea (5-10%)
Oil bathing

Steroids: (still) the most important weapon

Efficacy

class 1 (weak):
Hydrocortison,
Prednisolon,
Dexamethason

class 2 (moderate):

Prednicarbat	(Dermatop®)
Hydrocortisonbutyrat	(Alfason®, Laticort®)
Hydrocortisonbuteprat	(Neuroderm akut®)
Methylprednisolonaceponat	(Advantan®)
Hydrocortisonaceponat	(Retef AP®)
Triamcinolonacetonid	

class 3 (strong):

Mometasonfuroat	(Ecural®,Monovo®)
Fluticasonpropionat	(Flutivate®)
Betamethasonvalerat	
Fluocinolonacetonid	(Jellin®)
Fluprednidenacetat	(Decoderm®)
Diflucortolonvalerat	(Nerisona®)

class 4 (very strong):

Clobetasolpropionat	(Dermoxin®)

Anti-septic approaches with AD

- super-infected AD → antibiotic therapy:
  - Amoxicillin/clavulan acid (Co-Amoxi Mepha sirup) (1ml=80mg) 50-75mg/kg/Tag twice daily for 7 days
  - Flucloxacilline (Staphylex) 500 mg 2-2-2
  - Allergy to penicillin: clindamycine (Dalacin)
- Triclosan-containing lotions on a daily basis
  - Procutol®
  - Triclosan 1-2% in Lipikar Baume, Trixéra Balsam, Excipial U Lipolotio
- bleach baths?
  - product: Javelwasser from COOP
    - 2.5% Natriumhypochlorid → 200ml with 100L water
  - cave: do not mix with other additives

Metaanalysis of conventional systemic therapies of AD

Reference	Efficacy drug A a) Intervention b) Change in clinical signs	Efficacy drug B a) Intervention b) Change in clinical signs	Efficacy placebo a) Placebo b) Change in clinical signs
Berth-Jones[12]	a) AZA b) MI of 26% in SASSAD score at 8 wk		a) Placebo b) MI 3% in SASSAD score at 8 wk
Meggit[26]	a) AZA b) MI in of 37% in SASSAD score at 12 wk		a) Placebo b) MI of 20% in SASSAD score at 12 wk
Bemanian[11]	a) CsA b) MI of 68% in SCORAD at 12 wk	a) IVIG b) MI of 30% in SCORAD at 12 wk	
Czech[16]	a) CsA, 150 mg b) MI of 48% in TBSA at 8 wk	a) CsA, 300 mg b) MI of 59% in TBSA at 8 wk	
Granlund[17]	a) CsA b) MI of 54% in SCORAD at 8 wk	a) UVAB b) MI of 34% in SCORAD at 8 wk	
Haeck[18]	a) CsA b) MI of 17% in SCORAD score at maintenance phase (0-30 wk and 42% MI in SCORAD score including run-in phase of 6 wk (−6 wk to 30 wk)	a) EC-MPS MI of 0% in SCORAD at the maintenance phase (0-30 wk and 39% MI SCORAD including run-in phase of 6 wk (−6 wk to 30 wk)	

- clear 1st line recommendation: ciclosporine A (14 RCTs: consistent and high efficacy)
- 2nd line recommendation: azathioprine, but: less efficient and less evidence as compared to Ciclosporin
- 3rd line recommendation: methotrexate (different in US)
- Not sufficient data for a recommendation of MMF, IVIGs, systemic steroids

Roevkevich E at al, JACI 2014

Interleukin-4

- Initially described as a "B-cell stimulatory factor"
  Howard M et al. J Exp Med. 1982
- Produced by CD4+ T helper (T_H) cells, CD8+ T cells, eosinophils, basophils, natural killer T cells and activated mast cells.
  Röcken M et al. Immunol Today. 1996
- Pleiotropic cytokine expressed at high levels in the early phases of multiple acquired immune responses. Zhu J et al. Annu Rev Immunol. 2010
- Largely known for its capacity to initiate T_H2 cell differentiation, when acting directly on T cells.
  Paul WE et al. Nat Rev Immunol. 2010

http://en.wikipedia.org

First success: Dupilumab

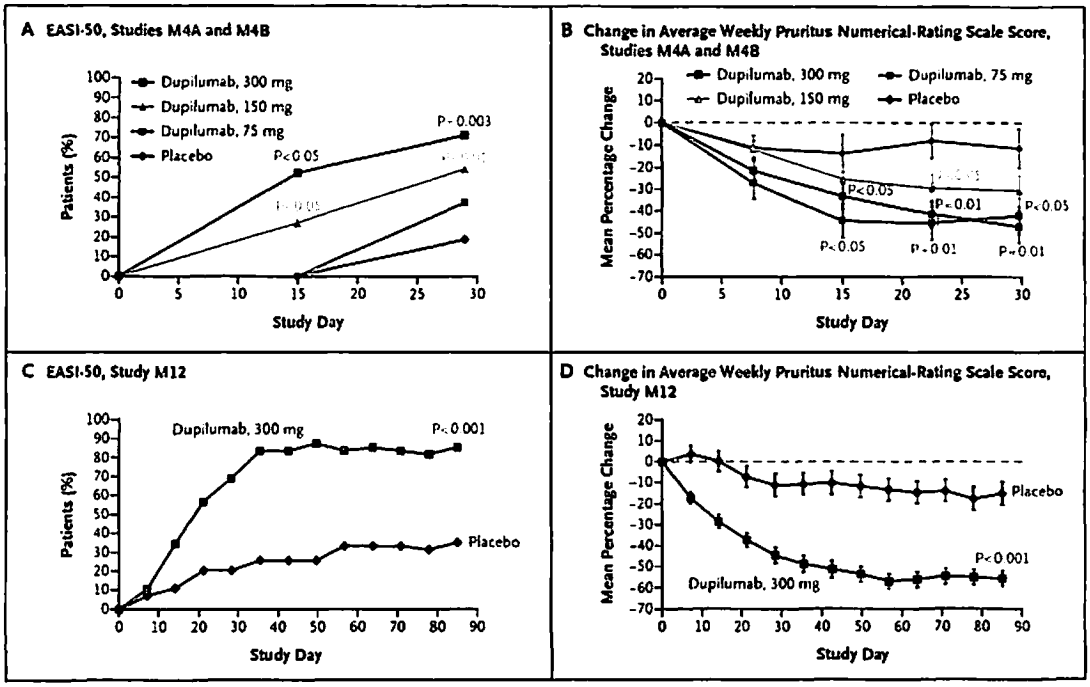
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis

Lisa A. Beck, M.D., Diamant Thaçi, M.D., Jennifer D. Hamilton, Ph.D., Neil M. Graham, M.D., Thomas Bieber, M.D., Ph.D., M.D.R.A., Ross Rocklin, M.D., Jeffrey E. Ming, M.D., Ph.D., Haobo Ren, Ph.D., Richard Kao, Dr.P.H., Eric Simpson, M.D., Marius Ardeleanu, M.D., Steven P. Weinstein, M.D., Ph.D., Gianluca Pirozzi, M.D., Ph.D., Emma Guttman-Yassky, M.D., Ph.D., Mayte Suárez-Fariñas, Ph.D., Melissa D. Hager, M.A., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Allen R. Radin, M.D.

First success: Dupilumab



Beck LA et al, N Engl J Med 2014

What´s in the pipeline?

Target	Biological	Level of evidence	Key outcome/ Reference
Th2-Immunity			
IL-4Rα	Dupilumab (further substances: AMG-317, Pitrakinra)	Phase III	EASI 50: 47/55
IL-5	Mepolizumab	Stopped after phase II	EASI 50: 0/18
IgE	Omalizumab (further substances: MEDI4212, QGE031)	Stopped after proof-of-concept	Heterogeneous reports ranging from EASI or SCORAD 50 0/20 to 21/21
CD20	Rituximab	Case series	EASI 50: 6/6, long-term: 0/2
IL-31	BMS-981164	Phase I ongoing	
IL-31R	CIM331	Phase II ongoing	
TSLP	AMG-157	Phase I completed	unpublished
CRTH2	QAW039	Phase II completed	unpublished
non-Th2-Immunity			
IL-1R1	Anakinra	Phase I completed	unpublished
IL-6	Tocilizumab	Case series	EASI 50: 3/3
IL-22	ILV-094	Phase II ongoing	
IL-23p40	Ustekinumab	Case series; phase II ongoing	Heterogeneous reports: successful versus non-effective
TNF-α	Etanercept	Case series	EASI 50: 0/2
IFN-γ		Phase III	EASI 50: 18/40

SSAI Swiss Society for Allergology and Immunology

19th Course: Allergy and Immunology Update (AIU)
Weekend January 20th to 22nd, 2017
Grindelwald, Hotel Sunstar and Gemeindesaal

Provocation in drug hypersensitivity: potential and limitations

Patrizia Bonadonna, MD CME
Allergy Unit, University Hospital of Verona *Italy*

Adverse Drug Reactions (ADRs):

- Affect:
  - 8% of the general population
  - 17%-25% in outpatient patients
  - 15 % in hospitalized patients

6.7% seriuos
0.32% fatality

Mortality for ADRs

ADRs is the IV° cause of death USA

- Toxic epidermal necrolysis
- Anaphylactic Shock
- Stevens- Johnson syndrome
- Drug Induced hypersensitivity Syndrome
- Other (vasculitis,kidney diseases, hepatotoxicity etc.)

JAMA 1998; 279: 1200–05

Adverse Drug Reactions:

1) Type A: Augmented

- Antihistamines: sleepiness
- NSAIDs: heartburn
- b adrenergic: tremors
- antibiotics : diarrhea
- calcium antagonists : ankle edema

ble. 80%

rmacological

2) Type B: Bizarre 15%

- dose-independent
- unpredictable

Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003

Drug Hypersensitivity Reactions

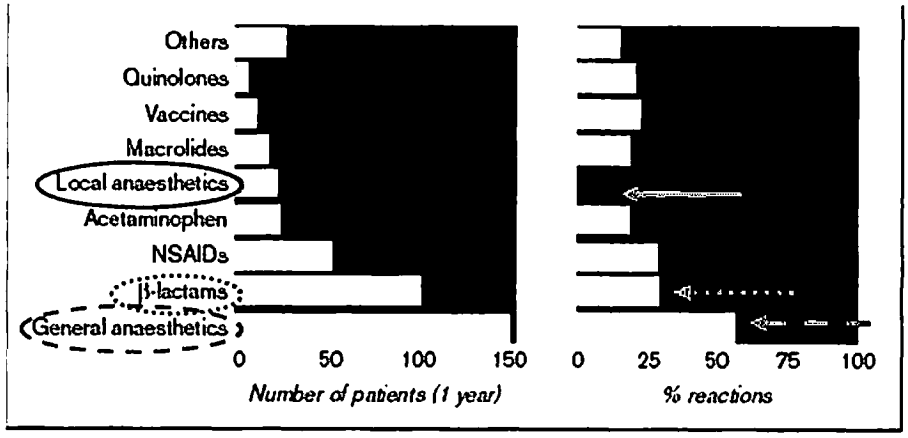
Drug Allergy

IgE-mediated drug allergy

Non-IgE-mediated drug allergy

Non Allergic Drug Hypersensitivity

P.Demoly. Et al. ACI International 1999



442 subjects with history of ADR

Underwent to skin test and provocation tests

40% YES DHR

60% NO DHR

898 adults with suspected drug-induced immediate-type hypersensitivity

→ 241 positive skin/drug provocation tests: **17.6%**

67 children, with parent- reported drug allergy

→ 3 positive skin/drug provocation tests: **5 %**

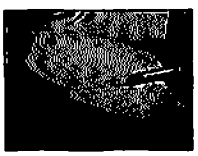
Messaad D Ann Intern Med 2004
Rebelo Gomes E. Clin Exp Allergy 2007

Diagnosis of Drug Hypersensitivity Reactions

History:

- symptomatology
- chronology of the symptoms
- all drug taken + cofactors
- the medical background of the patient
- ENDA questionnaire

Skin tests:



- Immediate DHR: Skin prick test and/ or Intradermal test
- Non immediate DHR Patch test and /or late reading IDT