Alergenová imunoterapie

„kauzální efekty léčby“

aneb „čím dříve, tím lépe“

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Datum vytvoření: 11/2018
Datum exspirace: 11/2019

„KONFLIKT ZÁJMŮ“

MUDr. Jiří Nevrlka

- není zaměstnancem, členem, ani podílníkem farmaceutické společnosti.
- historicky dostal finanční odměnu za přednášky a/nebo konzultace od farmaceutických společností: ALK-Abelló, Astra Zeneca, Berlin-Chemie Menarini Group, Chiesi, GSK, MSD, Orion Pharma, Sandoz, Stallergenes, TEVA, Zentiva.

PREZENTACE - OSNOVA

- SAIT – charakteristika a léčebné cíle

.. Přímý léčebný cíl vs. „Preventivní“ cíl = kauzální efekty léčby

- SAIT – kauzální efekty: tradiční pohled
- SAIT – kauzální efekty: revidovaný pohled

.. guidelines EAACI 2018, resp. rezhodnocení studií (EBM)

- SAIT – kauzální efekty: budoucí pohled
- SAIT – kauzální efekty: osobní pohled

SAIT - charakteristika

- **SAIT (specifická alergenová imunoterapie) je léčebný postup, při kterém se do organismu alergika v pravidelných časových intervalech vpravují přesně definované dávky terapeutických alergenů, na které je přecitlivělý.**

- **Cílem je snížit atopickou reaktivitu organismu na daný alergen(y) zásahem především do regulačních funkcí T lymfocytů** _ dochází k „přeladění“ imunitní odpovídavosti od typu TH2 /atopický/ na TH1 /normální/.

SAIT v léčbě alergie

Pozitivní anamnéza

(alergenu odpovídající klinika)

+

Pozitivní testace

(průkaz IgE senzibilizace na daný alergen)

–– prick testy a/nebo specifické IgE ––

SAIT (alergenová imunoterapie)

Léčbu SAIT CZ indikuje výhradně alergolog.

SAIT v léčbě PREalergie

SAIT před klinickou manifestací alergie (stadium ½-2) ?

½ st. 1/2. stádium = hraniční nebo mírně zvýšené hladiny některých rizikových faktorů

1.st. 1. stádium = preklinické alterace (změny na subcelulární úrovni)

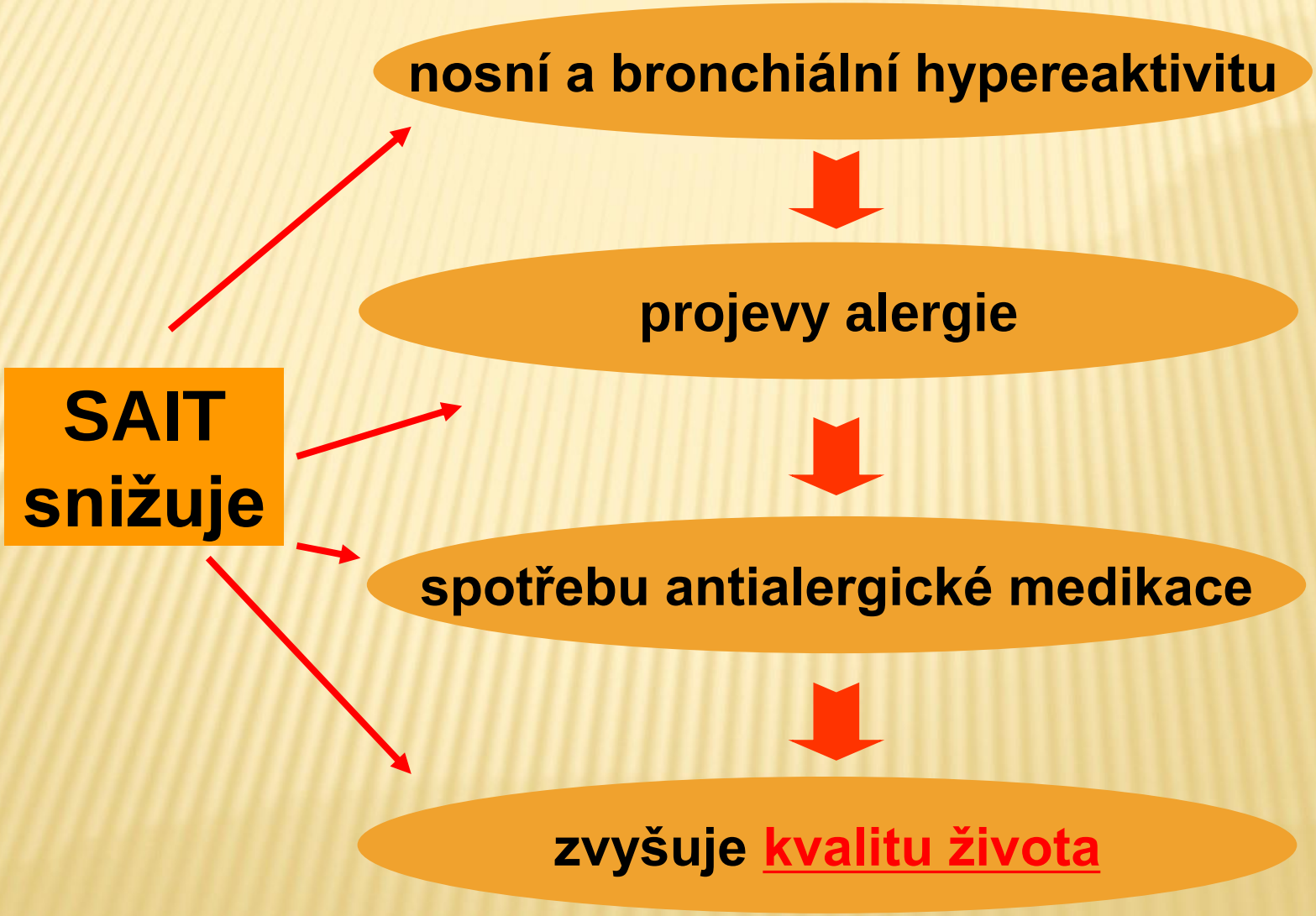
2.st. 2. stádium = subklinické alterace (labor. metodami nebo zátěžovými testy lze prokázat biochemické, buněčné nebo fyziologické změny)

zatím

NE

SAIT v léčbě alergie

SAIT – cíl _ léčebný



SAIT – cíl _ léčebný (př.Oralair)

Účinnost Oralair (Primární end point /ARTSS, DCS/ vs. Placebo %)

Study Phase	Primary end point	Treatment	Primary analysis set (n)	LS mean	LS mean difference vs placebo		p-value vs placebo*	Ref.
					Absolute point estimate (95% CI)	*Relative point estimate (%)*		
VO34.04	ARTSS	500 IR (4M)	143	3.74	-1.22 (-1.91, -0.53)	-24.7	0.0006	[45]
E		300 IR (4M)	136	3.58	-1.39 (-2.09, -0.69)	-28.2	0.0001	
a		100 IR (4M)	142	4.72	-0.26 (-0.95, 0.43)	-5.3	0.4606	
II		Placebo	148	4.93				
VO56.07A	ARTSS	300 IR	45	4.85	-1.97 (-2.99, -0.94)	-29.3	0.0003	[49]
Allergen-exposure cham		Placebo	44	6.87				
study								
adults								
I								
VO52.06	ARTSS	300 IR (4M)	131	3.25	-1.13 (-1.80, -0.46)	-25.5	0.0010	[50]
EU pedia		Placebo	135	4.51				
study								
III								
VO53.06#	AAdSS	300 IR (4M)	149	3.39	-1.82 (-2.61, -1.02)	-34.9	<0.0001	[28,51]
Long-term		300 IR (2M)	147	3.25	-1.96 (-2.76, -1.16)	-37.6	<0.0001	
effica		Placebo	165	5.21				
in ad								
III								
VO61.08	Daily CS§	300 IR (4M)	208	0.32	-0.13 (-0.19, -0.06)	-28.2	0.0003	[52]
US		ebo	228	0.45				
adu								
III								

Základní pro dospělé EU určení dávky v IR/tbl.

Provokační (komora)

Základní pro děti a dospívající EU

Dospělí EU/Canada - dlouhodobé efekty

Základní pro dospělé USA

DCS -29.6%

DCS -30%

DCS -16.4 .. -28.3%

DCS -28.2%

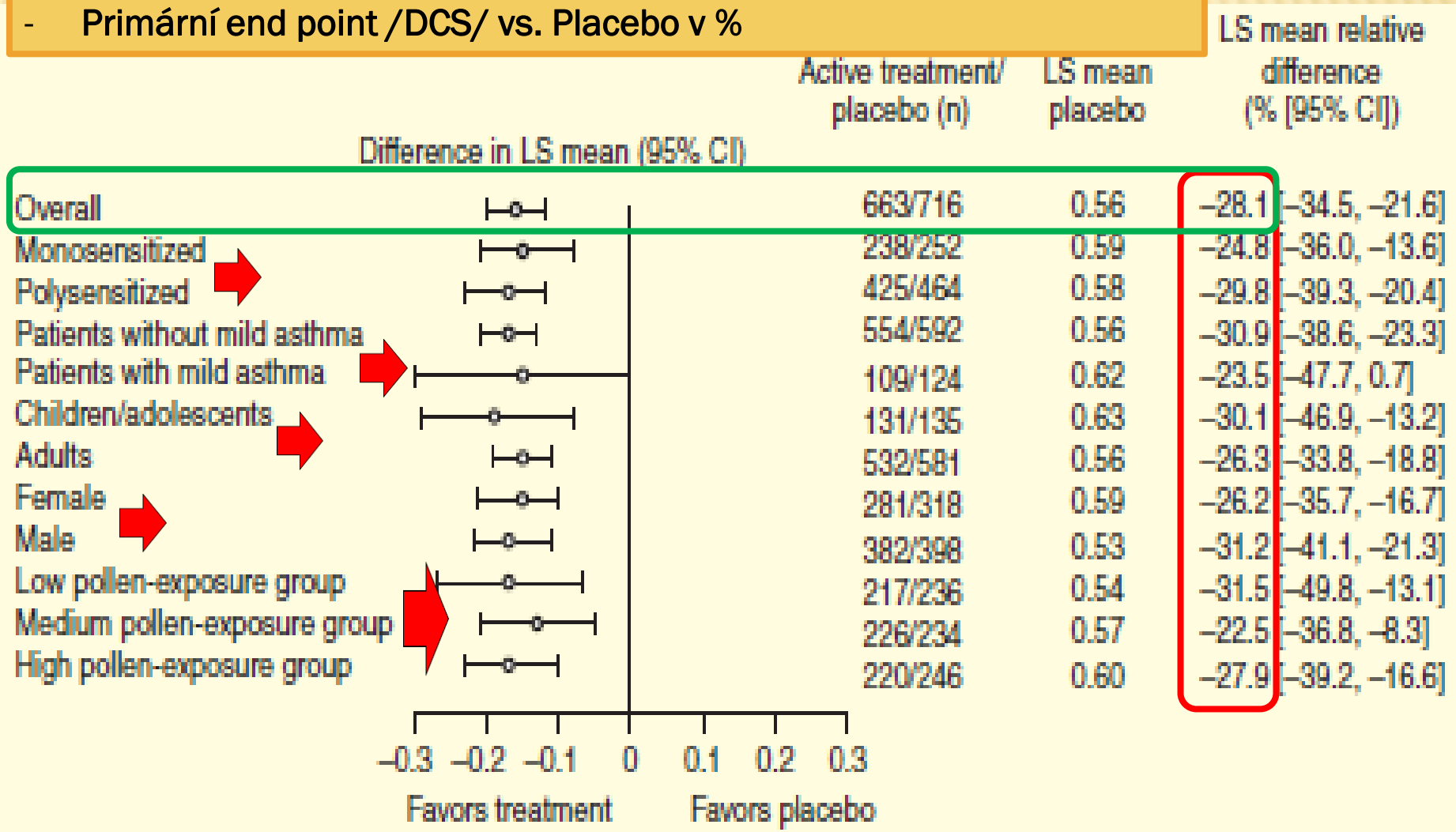
Sloučená analýza pro dávku min. 300 IR doložila 28.1% zlepšení (DCS) vůči placebu.

R.K. Zeldin et al. Efficacy of 5-grass pollen extract sublingual tablet in patients with grass pollen-associated allergic rhinoconjunctivitis assessed by Daily Combined Score: pooled study results. Abstract EAACI June 2014.

SAIT – cíl _ léčebný (př.Oralair)

Účinnost Oralair (Sloučená analýza pro dávku min. 300 IU)

- Různě definované skupiny pacientů
- Primární end point /DCS/ vs. Placebo v %



SAIT – cíl _ léčebný _ efektivita (př.Oralair)

Metaanalýza studií 2014 (Efekt různých typů léčby pylové alergie)

Symptomatická léčba: 29 publikací
AIT - SLIT : 10 publikací

21.223 pacientů

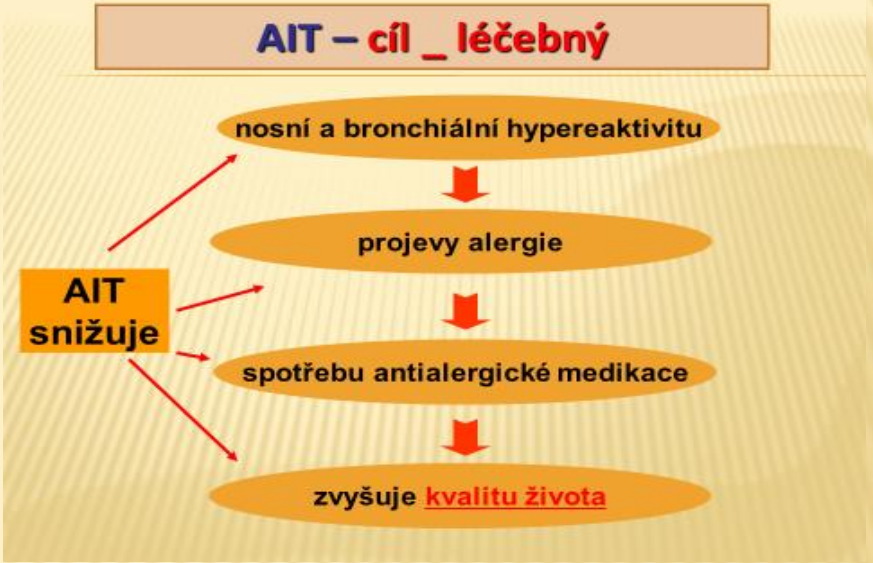
Efektivita léčby:	
5 trav SLIT tablety	29,6%
nazální steroidy	23,5%
bojínek SLIT tablety	19,2%
nazální azelastin/flutikazon	17,1%
antihistaminika p.os.	15,0 %
montelukast	6,5%

P.Devillier, JF Dreyfus, P.Demoly, MA Calderón: A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. BMC Medicine 2014, 12:71

SAIT
v „prevenci“ alergie

SAIT v léčbě alergie

Léčebný cíl



Preventivní cíl

= kauzální efekty léčby

SAIT kauzální - předpoklady

- **SAIT (specifická alergenová imunoterapie) je ..**
- **Cílem je snížit atopickou reaktivitu organismu na daný alergen(y) zásahem především do regulačních funkcí T lymfocytů** _ dochází k „přeladění“ imunitní odpovídavosti od typu TH2 /atopický/ na TH1 /normální/.

SAIT je kauzální léčbou (je léčbou samé podstaty alergie I.typu jako imunopatologického procesu).

SAIT
kauzální efekty
„tradiční pohled“

SAIT kauzální – tradiční pohled

- **SAIT má dlouhotrvající účinnost, efekty SAIT přetrvávají i po jejím ukončení.**

  Durham SR. et al. N Engl J Med 1999; 341: 468-75.
  Cools M. et al. Allergy 2000; 55:69-73.

- **SAIT chrání před progresí patofyziologického pochodu z alergické rýmy do astmatu.**

  Jacobsen L. Allergy 1997;52: 914-20.
  Moller C. et al. JACI 2002; 109:251-256.

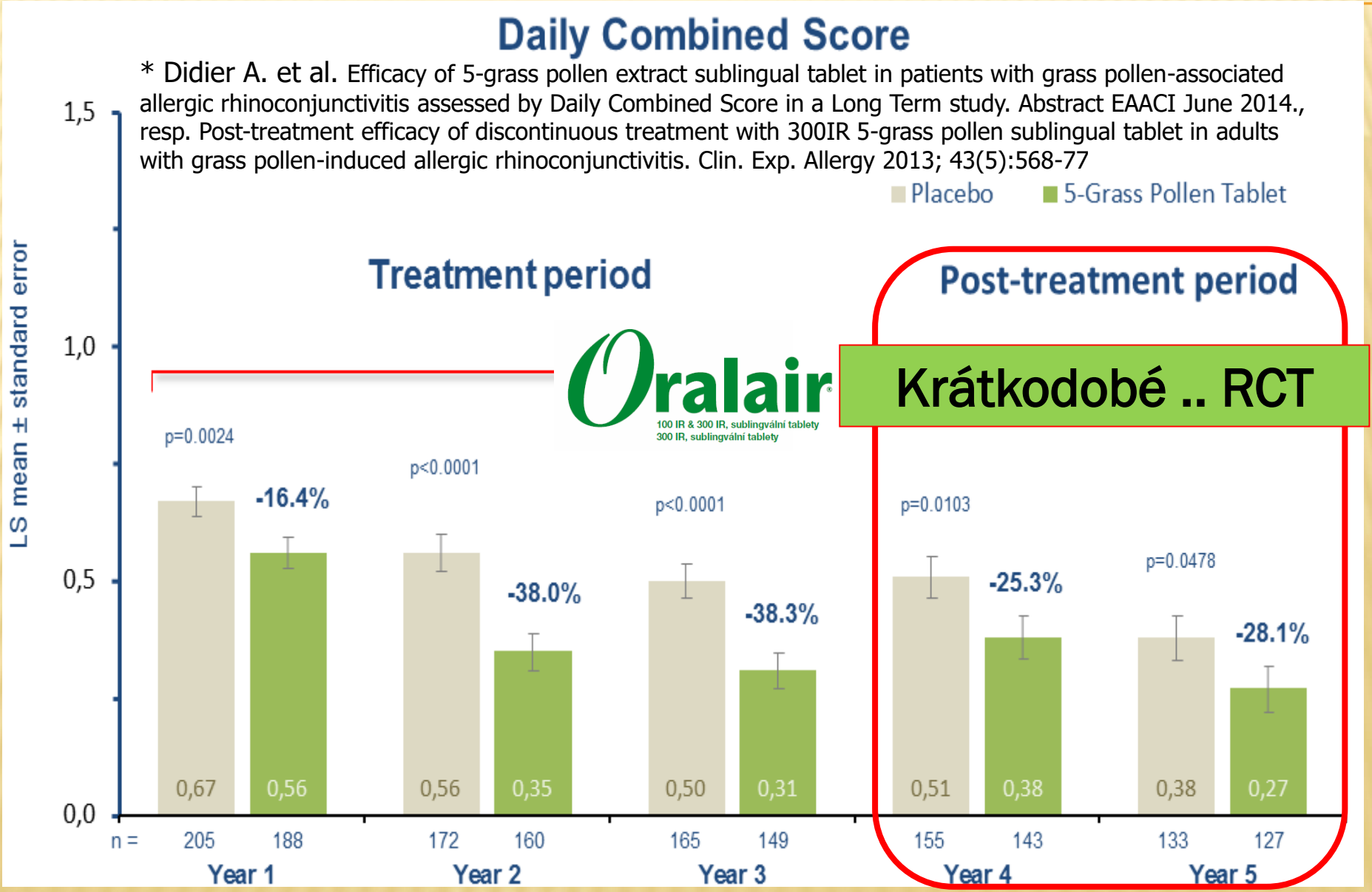
- **SAIT je prevencí vývoje od monosenzibilizace k alergenové polyvalentní senzibilizaci.**

  Des Roches A. et al. JACI 1997; 99:450-53.
  Pajno GB. et al. Clin Exp Allergy 2001;31:1392-97.

SAIT
kauzální efekty
..přetrvávání efektu

Durham SR. et al. N Engl J Med 1999; 341: 468-75.
Cools M. et al. Allergy 2000; 55:69-73.

SAIT – přetrvávání efektu krátkodobé („produkt“)

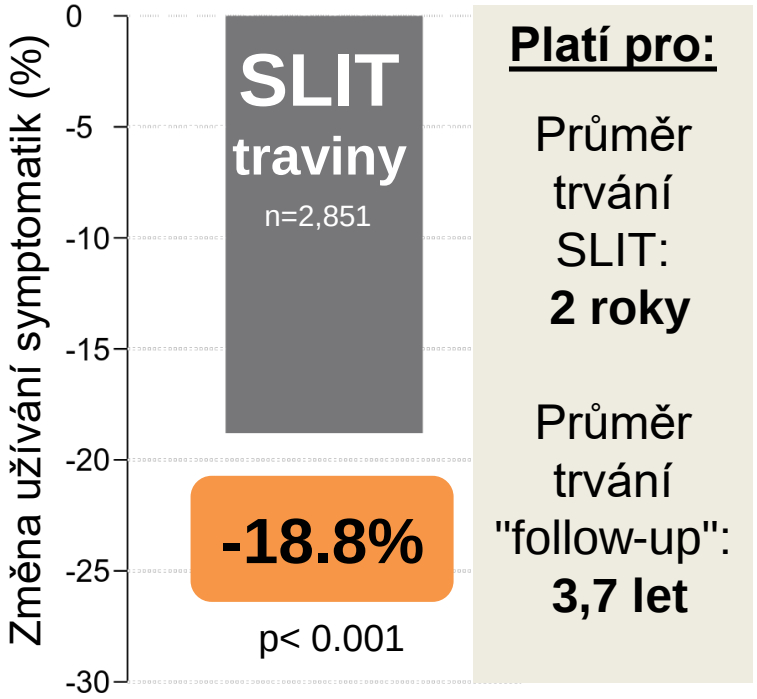


SAIT – přetrvávání efektu dlouhodobé („skupina“)

Dlouhodobé .. CBA

Změna užívání symptomatik (ad SAR traviny..V-VIII)

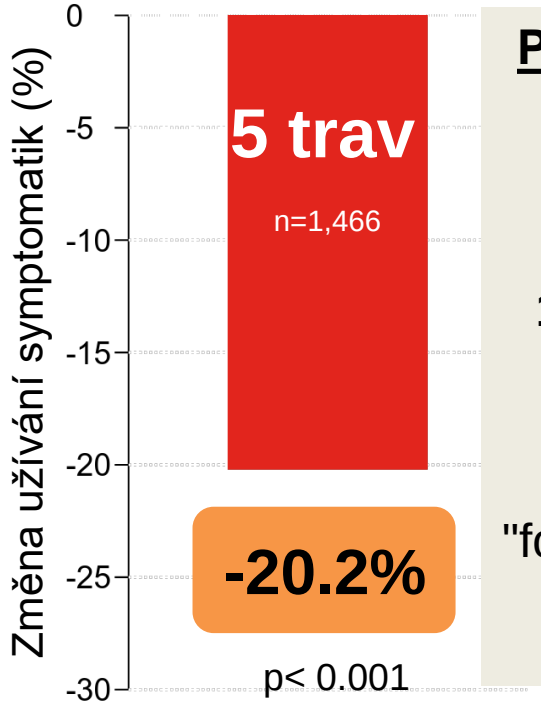
- ✓ jde o srovnání skupiny SLIT vs. skupina standard.farmakoterapie
- ✓ v době po skončení SLIT tbl. léčby (parametry viz níže)



Platí pro:

Průměr trvání SLIT: **2 roky**

Průměr trvání "follow-up": **3,7 let**



Platí pro:

Průměr trvání SLIT: **1.9 roku**

Průměr trvání "follow-up": **3,7 let**

1. Zielen S, et al. Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis. *Allergy*. 2017 May 31. doi: 10.1111/all.13213.
2. Wahn U, *et al*. Treatment with a 300 index of reactivity 5-grass pollen tablet is associated with long-term relief of allergic rhinitis: A retrospective real-life dataset subgroup analysis. 2017. *EEAC 2017*. Poster 1528

SAIT
kauzální efekty
..prevence progrese k AB

Jacobsen L. Allergy 1997;52: 914-20.
Moller C. et al. JACI 2002; 109:251-256.

Progrese od AR k AB - předpoklady

koncept jednotných dýchacích cest

Chronický respirační zánětlivý syndrom

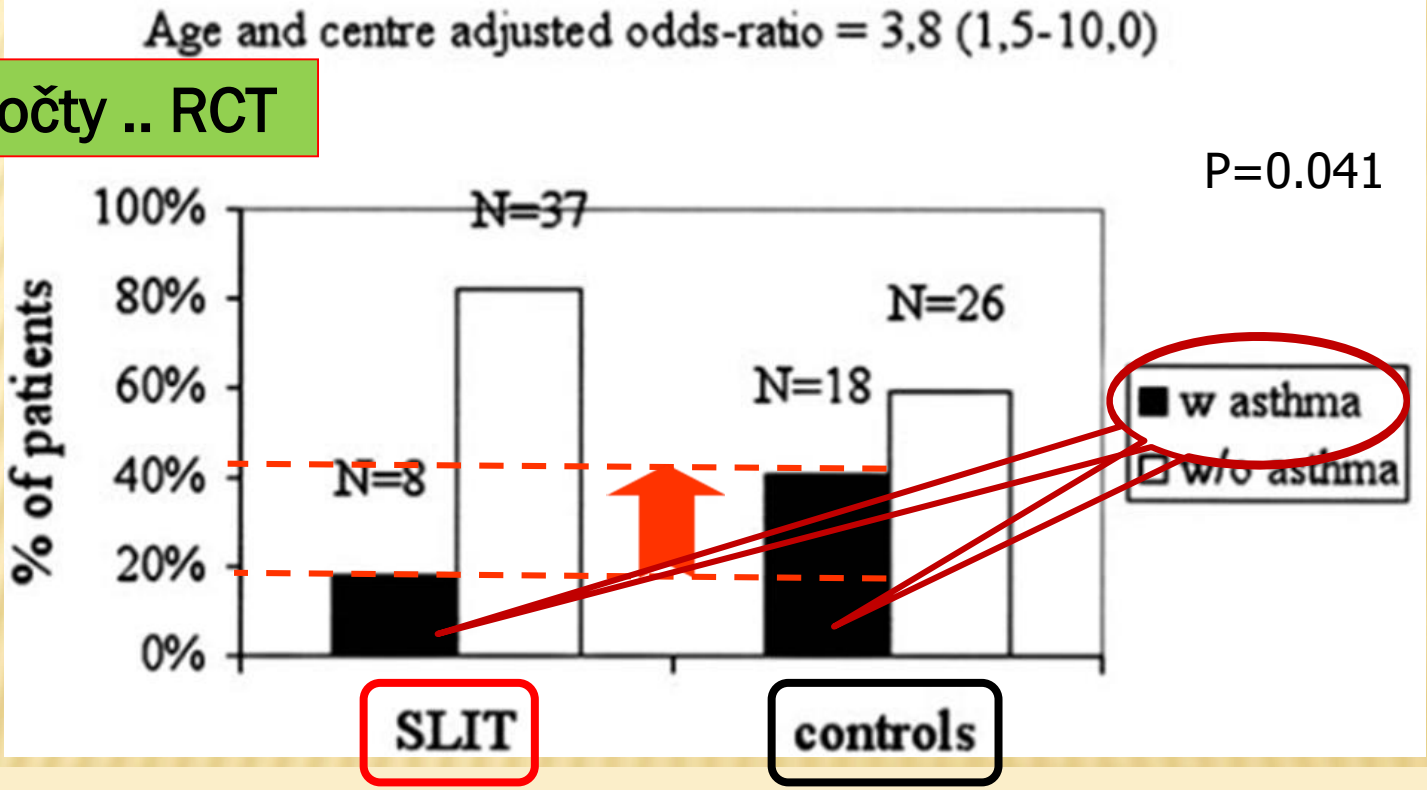
Alergická rýma
- u více než 85% astmatiků
Astma bronchiale
- u cca 50% pacientů s AR

Togias A. JACI 2003;111:1171.

SAIT – prevence progrese k AB (SLIT traviny)

Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis * Novembre E. et al. JACI 2004; 114(4): 851-857

Malé počty .. RCT



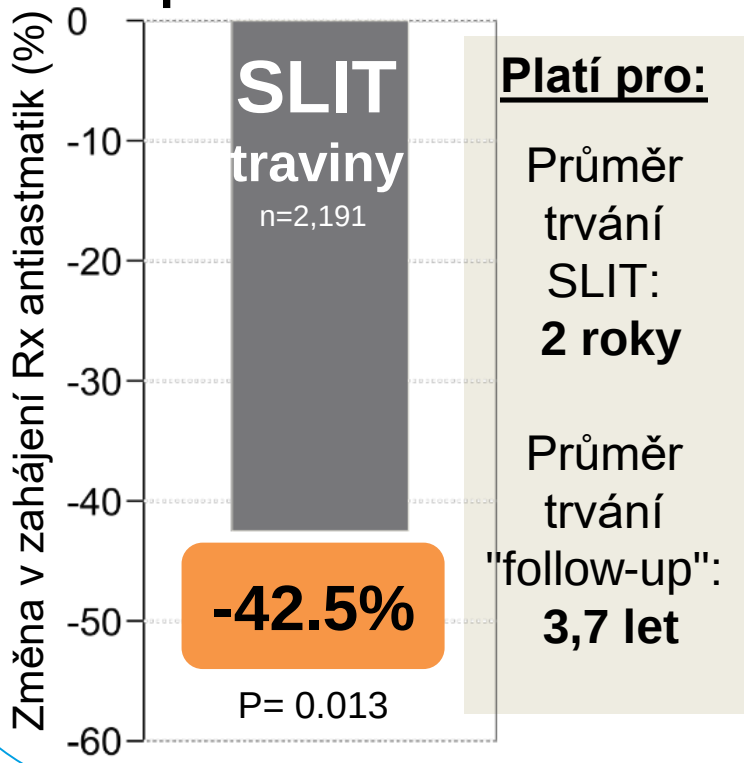
U dětí (5-14 let) se SAR byl při léčbě pylovou SLIT traviny po dobu 3 let významně nižší vznik AB (3,8x nižší riziko).

SAIT – prevence progrese k AB (SLIT traviny)

Velké počty .. CBA

Změna v zahájení předpisu antiastmatik (SABA, IKS,..)

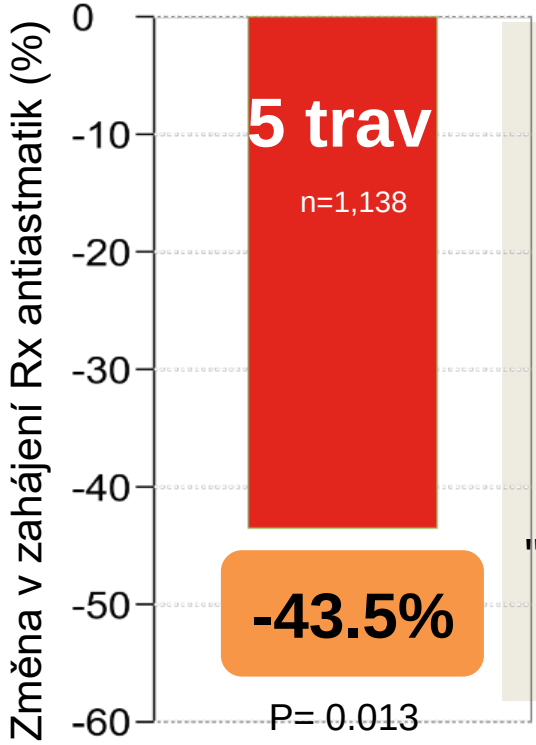
- ✓ **jde o srovnání skupiny SLIT vs. skupina standard.farmakoterapie**
- ✓ **v době po skončení SLIT tbl. léčby (parametry viz níže)**



Platí pro:

Průměr trvání SLIT: **2 roky**

Průměr trvání "follow-up": **3,7 let**



Platí pro:

Průměr trvání SLIT: **1.9 roku**

Průměr trvání "follow-up": **3,7 let**

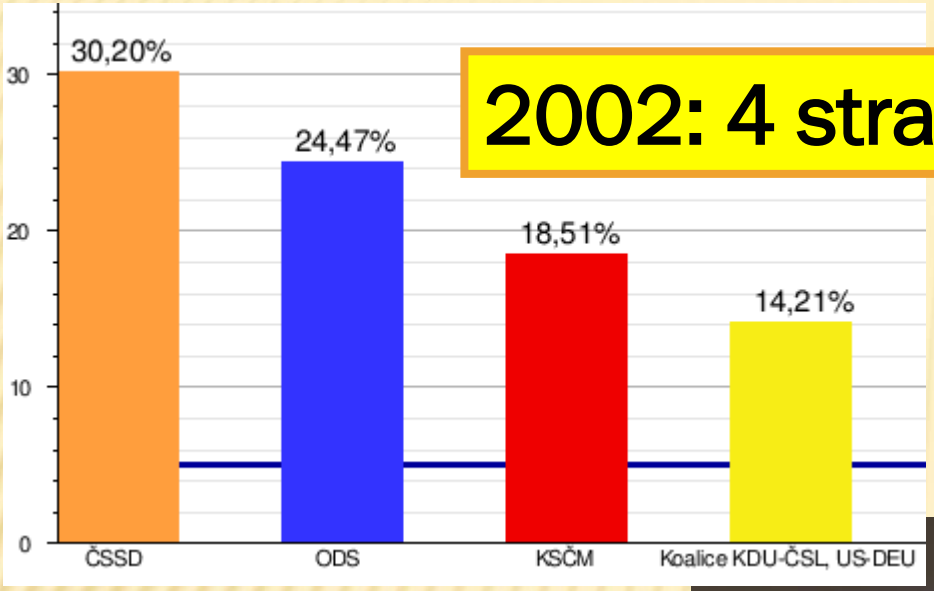
1. Zielen S, et al. Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis. *Allergy*. 2017 May 31. doi: 10.1111/all.13213.
2. Devillier P, *et al*. A treatment with 300 IR 5-grass pollen tablet is assocated with a reduction of asthma onset and a reduction of its progression. *EAACI 2017*. Poster 1534.

SAIT
kauzální efekty

..prevence progrese k polysenzibilizaci (spreading)

Des Roches A. et al. JACI 1997; 99:450-53.
Pajno GB. et al. Clin Exp Allergy 2001;31:1392-97.

Spreading .. „šíření“



2002: 4 strany

Volby do parlamentu CZ

2017: 9 stran

Progrese k polysenzibilizaci

Klasický pohled

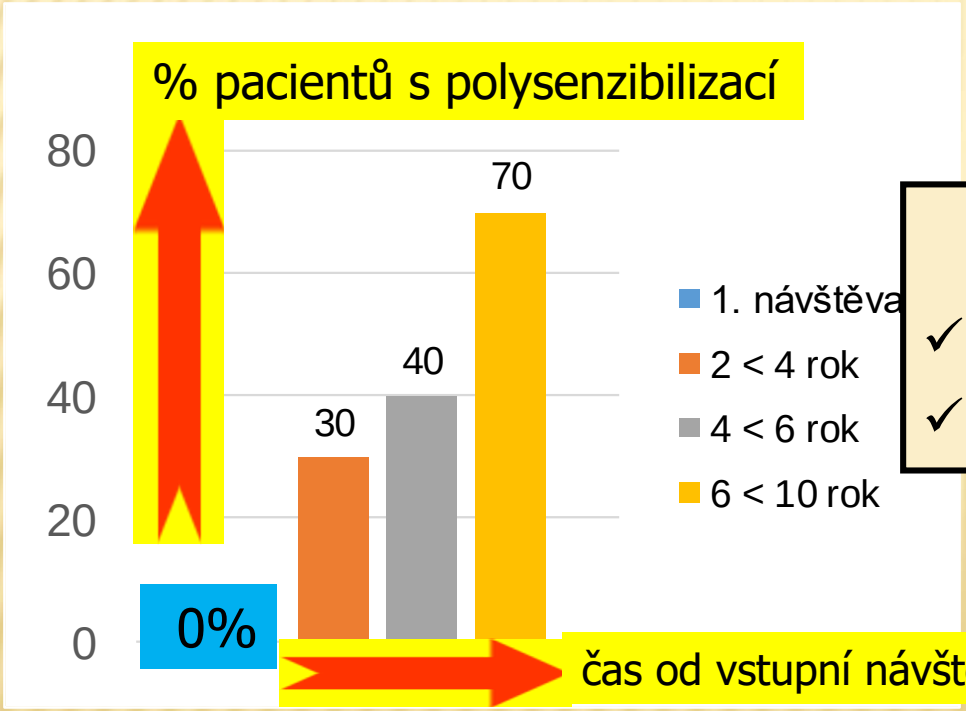
.. různé alergenové zdroje

CRD pohled

.. v rámci 1 alergenového zdroje

Progrese k polysenzibilizaci – klasický pohled

Age-dependent tendency to become sensitized to other classes of aeroallergens in atopic asthmatic children * Silvestri M. et al. Ann Allergy Asthma Immunol 1999; 83(4): 335-340.



„Trigerring role“:

- ✓ **Roztoči** (do 6 let 45.4% /59 ze 130 pac./)
- ✓ **Pyly** (do 6 let 32.1% /9 z 28 pac./)

U dětí (1.5-8 let) s AB a monosenzibilizací se vyvíjí v čase polysenzibilizace (do 6 let u více než 40%, do 10 let u více než 70%).

AIT – prevence spreadingu (klasicky)

Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study * Purello-D'Ambrosio F. et al. Clin.Exp.All. 2001; 31: 1295-1302.

Retroperspektivní studie – 8396 pacientů (7182 SAIT), různé alergeny, AR i AR společně s AB. Léčba SAIT 4 roky, posuzováno po 4 (T1) a 7 letech (T2).

	Number of patients	Polysensitized T1 (%)	Polysensitized T2 (%)
SAIT léčba			
Subgroup A1 (rhinitis)	2938	620 (21.10)	702 (23.89)
Subgroup A2 (asthma and rhinitis)	4244	1086 (25.59)	1234 (29.07)
Group A (total)	7182	1706 (23.75)	1936 (26.96)
bez SAIT			
Subgroup B1 (rhinitis)	499	318 (63.72)	356 (71.34)
Subgroup B2 (asthma and rhinitis)	715	508 (71.05)	576 (80.56)
Group B (total)	1214	826 (68.04)	932 (76.77)

SAIT bránila rozvoji polysenzibilizace v čase u AR±AB

(při 4-leté léčbě SAIT bylo po celkem 7 letech /tj. 4+3/ postiženo 27% pacientů SAIT léčených vs. 77% pacientů SAIT NEléčených).

Progrese k polysenzibilizaci

Klasický pohled

.. různé alergenové zdroje

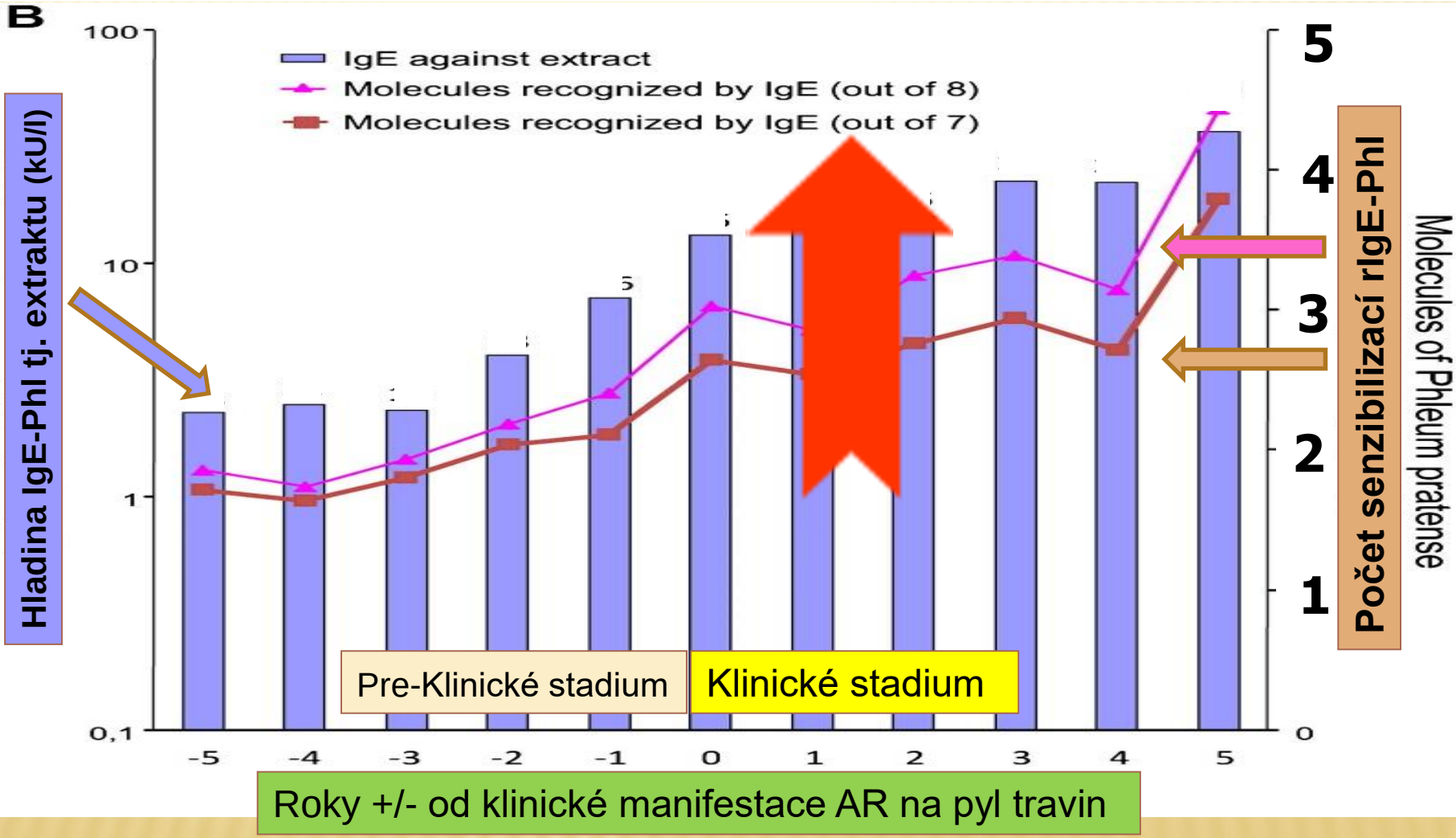
CRD pohled

.. v rámci 1 alergenového zdroje

.. molecular spreading

Progrese k polysenzibilizaci – CRD pohled

Hatzler L, Penatta V et al. Molecular spreading and predictive value of preclinical IgE response to Phleum pratense in children with hay fever. JACI 2012, 130:894-901



Progrese k polysenzibilizaci – CRD pohled

Matricardi PM. *Třídění IgE-odpovědí do skupin podle molekulárních profilů a jeho možné důsledky pro specifickou imunoterapii.* Curr Opin Allergy Clin Imun/CS (2014)

- **IgE odpověď se objevuje v dětství jako jednoduchá a slabá a u většiny pacientů se stává v čase složitější a silnější.**

- ***V dospělosti je IgE-odpověď u každého pacienta stabilní charakteristikou „jako otisk prstu“.*** ?!

SAIT
kauzální efekty
„revidovaný pohled“

Dnes: EBM

.. RCT: Evidence level I

→ doporučení grade A (silné)

Dnes: EBM

.. RCT: Evidence level I → doporučení grade A (silné)

Rizika zámořských plaveb - KURDĚJE

"Námořníci, jejichž nemoc je už v pokročilém stadiu, zůstanou na tomhle ostrově. Vy ostatní, kteří jste na tom zdravotně lépe, pokračujte se mnou v plavbě směrem k ústí řeky San Lorenzo." kapitán Jacques Cartier 1534

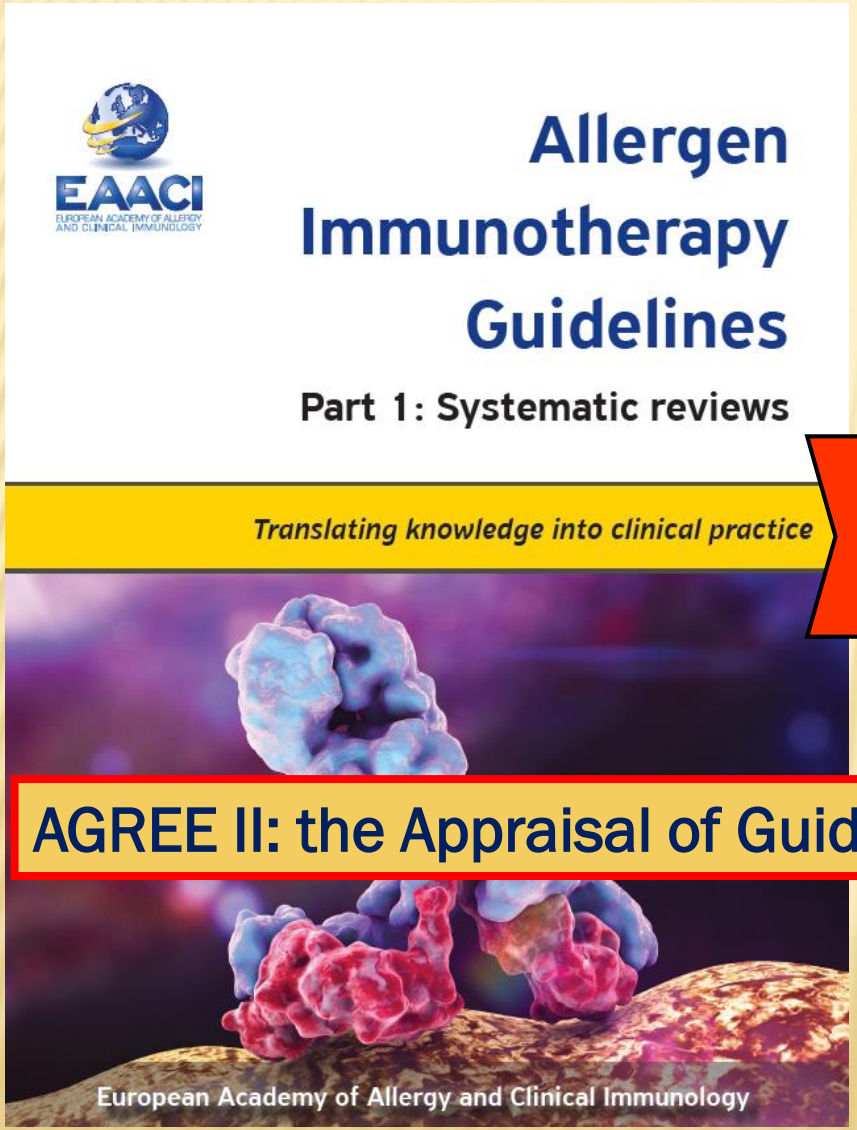
- Cartierova zpráva a lékařské kapacity

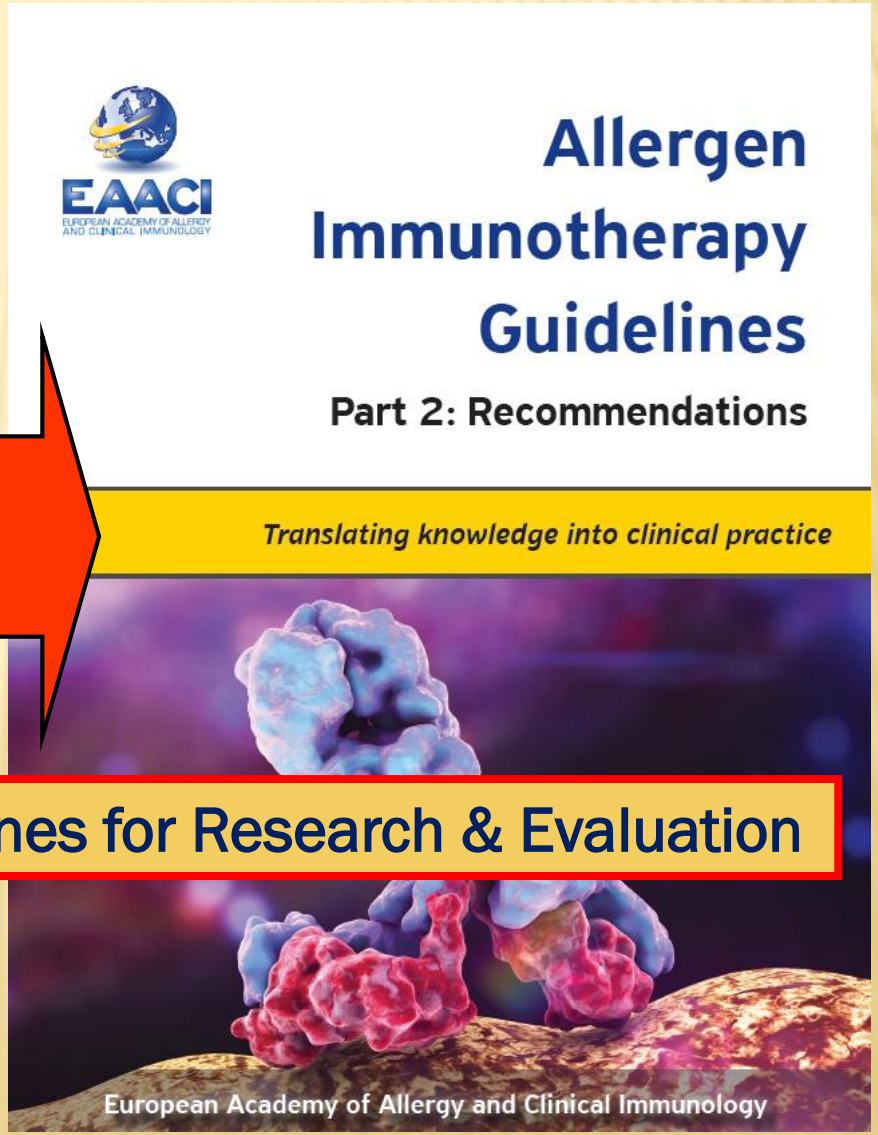
- „vždyť přece každý ví, že kurděje jsou nevyléčitelné"

- James Lind 1747

- „ zázračná moc citrusových plodů"

SAIT kauzální – přehodnocení EBM





AGREE II: the Appraisal of Guidelines for Research & Evaluation

SAIT v prevenci alergie – EAACI guidelines 2018

http://www.eaaci.org/resources/guidelines/ait-guidelines-part-2.html

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergen Immunotherapy Guidelines

Part 2: Recommendations

Translating knowledge into clinical practice

1

EAACI GUIDELINES ON ALLERGEN IMMUNOTHERAPY

PREVENTION OF ALLERGY

Susanne Halken[1], Desiree Larenas-Linnemann[2], Graham Roberts[3], Moises A Calderón[4], Elisabeth Angier[5], Oliver Pfaar[6,7], Dermot Ryan[8], Ioana Agache[9], Ignacio J Ansotegui[10], Stefania Arasi[11,12], George Du Toit[13], Montserrat Fernandez-Rivas[14], Roy Gerth van Wijk[15], Marek Jutel[16,17], Jörg Kleine-Tebbe[18], Susanne Lau[12], Paolo M Matricardi[12], Giovanni B Pajno[11], Nikolaos G Papadopoulos[19,20], Martin Penagos[4], Alexandra F Santos[13], Gunter J Sturm[21], Frans Timmermans[22], Ronald van Ree[23], Eva-Maria Varga[24], Ulrich Wahn[12], Maria Kristiansen[25], Sangeeta Dhami[26], Aziz Sheikh[8], Antonella Muraro[27]

SAIT v prevenci alergie – síla důkazů a doporučení

Recommendations for individuals with manifest allergic disease(s), e.g. allergic rhinitis	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In children and adolescents with AR and grass/ birch pollen allergy, who are sub-optimally controlled despite appropriate treatment with antihistamines / nasal corticosteroids, a 3 year course of AIT (SCIT or SLIT) can be recommended for the short-term (i.e. < 2 years post AIT) prevention of the onset of asthma in addition to the sustained effect on AR symptoms and medication use.	I	A	Moderate recommendation: Based on consistent significant results from 2 moderate (41, 43) and 2 high risk of bias (40, 42) RCTs and some CBA studies	The indication should be discussed with the patients / families including the asthma preventive effect as well as the effect on AR and risk of adverse effects, costs and preferences	Möller1986 (41), Möller2002 (40), Novembr 2004 (43), Marogna 2008 (42), Kristiansen 2017 (25
In children and adolescents with AR and grass/ birch pollen allergy, no recommendation can currently be made in favor of or against the	I	B	Weak recommendation: Based on consistent results from 2 high risk of bias RCTs	In the Valovirta 2017 (50) study no effect on the primary asthma outcome	Jacobsen 2007 (46), Song 2014 (47), Valovirta 2017 (50), Kristiansen 2017 (25)
demonstrated reversibility			analyses being not significant due to the latter study	reversibility. More data is needed	
In children and adolescents with AR and grass/ birch pollen allergy, the use of AIT (SCIT or SLIT) may be recommended for the long-term (≥ 2 years post AIT prevention of the onset of asthma symptoms and medication use	I	B	Weak -moderate recommendation: Based on consistent results from 2 high risk of bias RCTs (46) (47) and secondary outcomes in 1 low risk of bias RCT (50),	In the Valovirta 2017 (50) study a significant preventive effect on the secondary outcomes asthma symptoms and medication was found. More data is needed	Jacobsen 2007 (46), Song 2014 (47), Valovirta 2017 (50),

Krátkodobá (do 2 let)
Grade A (střední doporučení)

AR na pyly břízy či travin a prevence AB – děti a dospívající

Dlouhodobá (nad 2 roky)
Grade B (slabé až střední doporučení)

Table 3 AIT for prevention: recommendations for school-age children, adolescents and adults with allergic rhinitis (AR) or asthma

Recommendations for individuals with manifest allergic disease(s), e.g. allergic rhinitis	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In children and adolescents with AR and allergy to house dust mites or other allergens except for birch/grass pollen, no recommendation can currently be made in favor of or against the use of AIT (SCIT or SLIT) for the short-term (i.e. < 2 years post AIT) or long-term (i.e. ≥ 2 years post AIT) prevention of the onset of asthma	I	B	Weak recommendation: Based on inconsistent results from 1 high (42) and 1 low risk of bias RCT (38)	Only HDM, parietaria and mix of these and grass/ birch pollen investigated. More data is needed	Marogna 2008 (42), Crimi 2004 (39), Grembiale 200((38), Kristiansen 2017 (25)
In adults with AR and house dust mite or pollen allergy, no recommendation can currently be made in favor of or against the use of AIT (SCIT or SLIT) for the short-term (i.e. < 2 years post AIT) or long-term (i.e. ≥ 2 years post AIT prevention of the onset of asthma		B	Weak recommendation: Based on 1 small moderate risk of bias study (39)	Only SCIT with Parietaria Judaica investigated. More data is needed	Crimi 2004 (39)
In children or adults with AR and/or asthma, AIT cannot currently be recommended for the prevention of new sensitizations,		B	Weak recommendation: Based on inconsistent results from 4 high (42, 47, 60, 69), 2 moderate (59, 68) and 3 low risk of bias (55, 57, 58) RCTs		Marogna 2004 (60), Marogna 2008 (42), Dominicus 2012 (69), Song 2016 (47), Pifferi 2002 (59), Limb 2006 (68), Garcia 2010 (57), Szepfalusi 2014 (58), Zolkipli 2015 (55), Kristiansen 2017 (25)

Grade B – slabé doporučení

Prevence AB: HDM a jiné alergeny – děti a dospívající

Prevence AB: Všeobecně - dospělí

Prevence spreadingu: Všeobecně

SAIT v prevenci alergie – síla důkazů a doporučení

SAIT v prevenci alergie – EAACI guidelines 2018

Box 4 Summary

- A three year course of AIT (SCIT or SLIT) can be considered in children with moderate to severe AR and grass/birch pollen allergy, not sufficiently controlled with optimal pharmacotherapy, for
  - Treatment of AR with a sustained effect on symptoms and use of medication beyond cessation of AIT
  - Short-term (i.e. up to 2 years post-treatment) prevention of the onset of asthma in addition to improving the control of AR. Moreover, some studies indicate that this asthma preventive effect is maintained over a longer period as evaluated by symptoms and medication use
- Only AIT products with documented effect in patients with the relevant pollen allergy should be used and a product specific evaluation of clinical efficacy and preventive effects is recommended
- Before initiating AIT the possible benefits including the beneficial effects on controlling AR symptoms and the asthma preventive effect, disadvantages, potential harms, patients' preferences (SCIT or SLIT-tablets/ SLIT-drops), patients' adherence to treatment and costs should be discussed with the patient / family on an individual basis
- There is an urgent need for more high-quality clinical trials on prevention in AIT and more high quality evidence.

Box 5 Key messages for primary care about referral to allergy services

- AIT have a role in delaying/preventing progression from seasonal AR/ARC to asthma
  - Primary care teams should consider early referral of children with troublesome AR in spite of pharmacotherapy with antihistamine and or nasal corticosteroids for a specialist assessment with a view to considering AIT to improve control of AR and also simultaneously delay/prevent asthma
  - Patients should be considered as "individuals" during the assessment to prescribe AIT, they all have to be aware of the potential benefits, risks and costs of AIT
- AIT may be indicated in those individuals with perennial AR on clinical grounds but not only for delaying/preventing progression to asthma (this preventive effect needs to have high quality evidence)
- Recommendations cannot currently be made for AIT to prevent: (i) allergic parents who would be interested in receiving AIT to prevent allergy in their offspring; (ii) healthy infants/children; (iii) infants/children with AD and/or food allergy

SAIT kauzální – přehodnocení EBM

http://www.eaaci.org/resources/guidelines/ait-guidelines-part-1.html

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

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Part 1: Sys

Translating knowle

Pediatric Allergy and Immunology

ORIGINAL ARTICLE EPID

Allergen immunotherapy for the prevention of allergy: A systematic review and meta-analysis

Maria Kristiansen[1,*], Sangeeta Dhami[2,*], Gopal Netuveli[3], Susanne Halken[4], Antonella Muraro[5], Graham Roberts[6,7,8], Desiree Larenas-Linnemann[9], Moises A. Calderón[10], Martin Penagos[10], George Du Toit[11,12], Ignacio J. Ansotegui[13], Jörg Kleine-Tebbe[14], Susanne Lau[15], Paolo Maria Matricardi[16], Giovanni Pajno[17], Nikolaos G. Papadopoulos[18,19], Oliver Pfaar[20,21], Dermot Ryan[22], Alexandra F. Santos[10], Frans Timmermanns[23], Ulrich Wahn[16] & Aziz Sheikh[22]

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To cite this article: Kristiansen M, Dhami S, Netuveli G, Halken S, Muraro A, Roberts G, Larenas-Linnemann D, Calderón MA, Penagos M, Du Toit G, Ansotegui IJ, Kleine-Tebbe J, Lau S, Matricardi PM, Pajno G, Papadopoulos NG, Pfaar O, Ryan D, Santos AF, Timmermanns F, Wahn U, Sheikh A. Allergen immunotherapy for the prevention of allergy: A systematic review and meta-analysis. *Pediatr Allergy Immunol* 2017: **28**: 18–29.

Keywords
allergen immunotherapy; allergic diseases; allergy; atopy; prevention; sensitization

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Accepted for publication 17 September 2016

DOI:10.1111/pai.12661

Abstract

Background: There is a need to establish the effectiveness, cost-effectiveness, and safety of allergen immunotherapy (AIT) for the prevention of allergic disease.
Methods: Two reviewers independently screened nine international biomedical databases. Studies were quantitatively synthesized using random-effects meta-analyses.
Results: A total of 32 studies satisfied the inclusion criteria. Overall, meta-analysis found no conclusive evidence that AIT reduced the risk of developing a first allergic disease over the short term (RR = 0.30; 95% CI: 0.04–2.09) and no randomized controlled evidence was found in relation to its longer-term effects for this outcome. There was, however, a reduction in the short-term risk of those with allergic rhinitis developing asthma (RR = 0.40; 95% CI: 0.30–0.54), with this finding being robust to a pre-specified sensitivity analysis. We found inconclusive evidence that this benefit was maintained over the longer term: RR = 0.62; 95% CI: 0.31–1.23. There was evidence that the risk of new sensitization was reduced over the short term, but this was not confirmed in the sensitivity analysis: RR = 0.72; 95% CI: 0.24–2.18. There was no clear evidence of any longer-term reduction in the risk of sensitization: RR = 0.47; 95% CI: 0.08–2.77. AIT appeared to have an acceptable side effect profile.
Conclusions: AIT did not result in a statistically significant reduction in the risk of developing a first allergic disease. There was, however, evidence of a reduced short-term risk of developing asthma in those with allergic rhinitis, but it is unclear whether this benefit was maintained over the longer term. We are unable to comment on the cost-effectiveness of AIT.

1

RGEN IMMUNOTHERAPY
EVENTION OF ALLERGY

IEW AND META-ANALYSIS

pal Netuveli[3], Susanne Halken[4], Antonella Muraro[5], Graham
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be[14], Susanne Lau[15], Paolo Maria Matricardi[16], Giovanni
er Pfaar[20,21], Dermot Ryan[22], Alexandra F. Santos[11,12], Frans
[3], Ulrich Wahn[16], Aziz Sheikh[22]

Kristiansen M et al. Allergen immunotherapy for the prevention of allergy: A systematic review and meta-analysis. PAI 2017; 28(1): 18-29.

SAIT kauzální – přehodnocení EBM

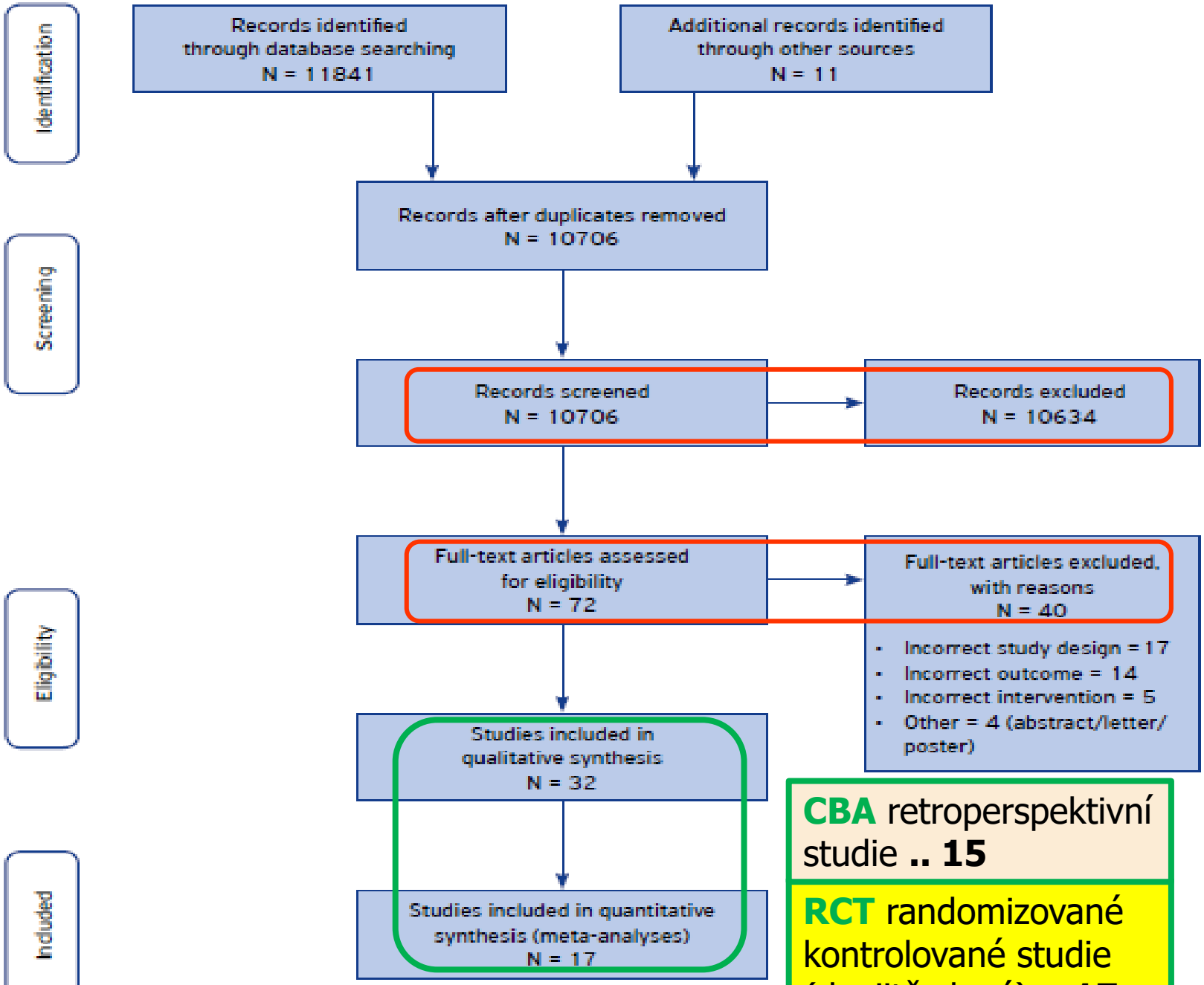


Figure 2 PRISMA flow diagram

CBA retroperspektivní studie .. **15**

RCT randomizované kontrolované studie (dvojitě slepé) .. **17**

výklad schémat EAACI SAIT guidelines

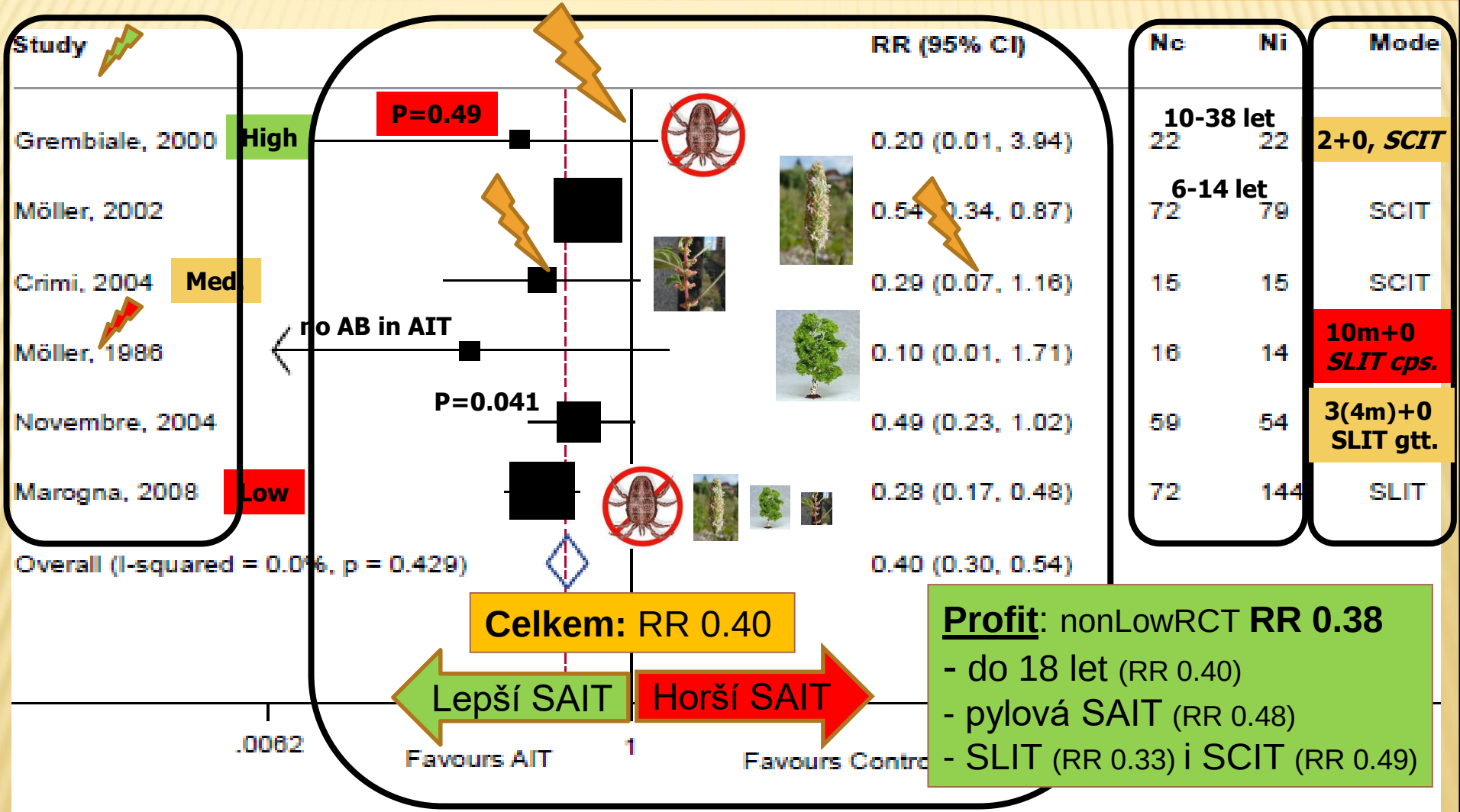


Figure 4 Random-effects meta-analysis of effectiveness of AIT in short-term prevention of asthma in those with allergic rhinitis. Nc = number in control group; Ni = number in intervention group; mode = route of administration of AIT.

SAIT – prevence vzniku alergie
(manifestace prvního alergického onemocnění)

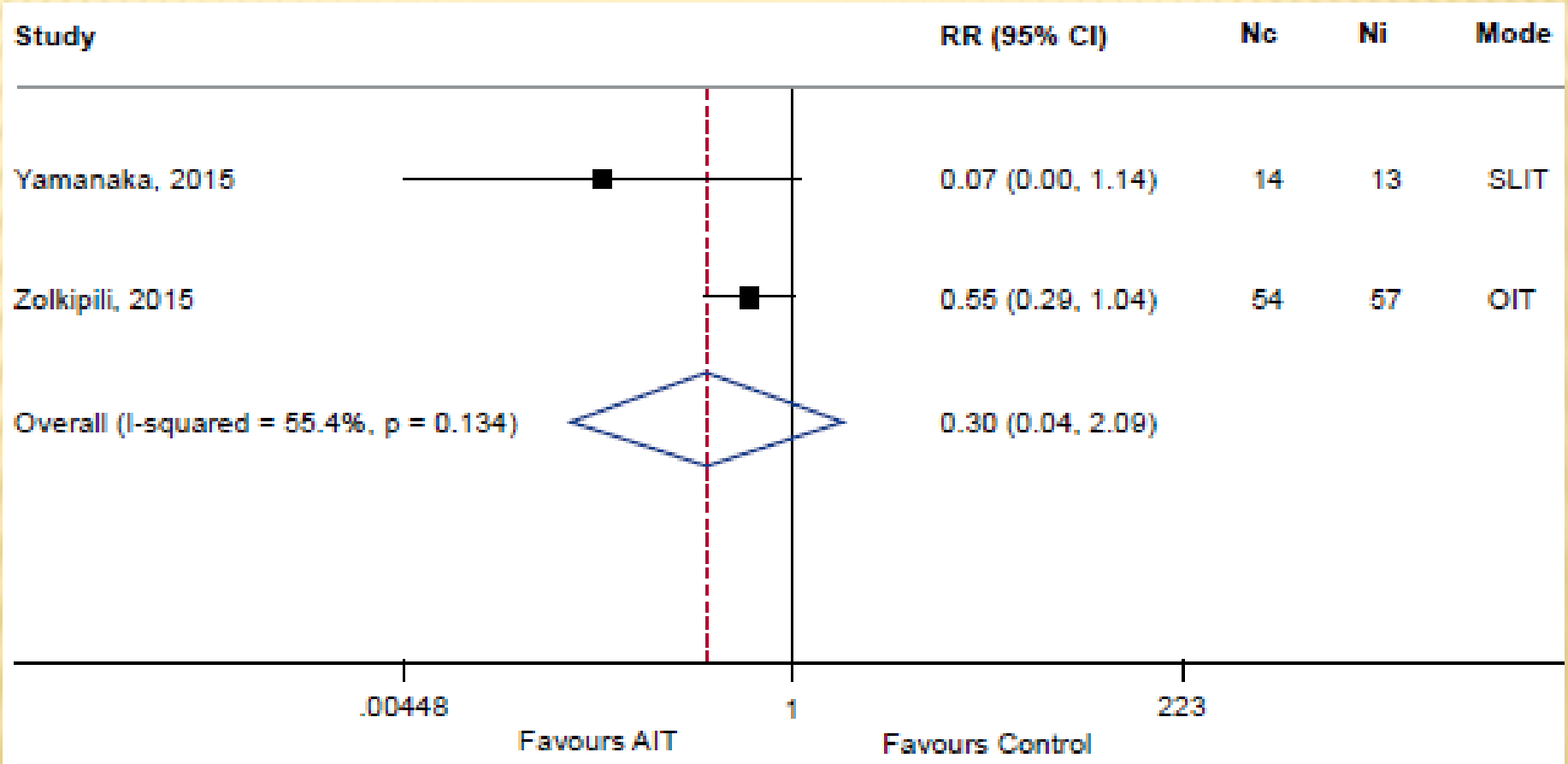
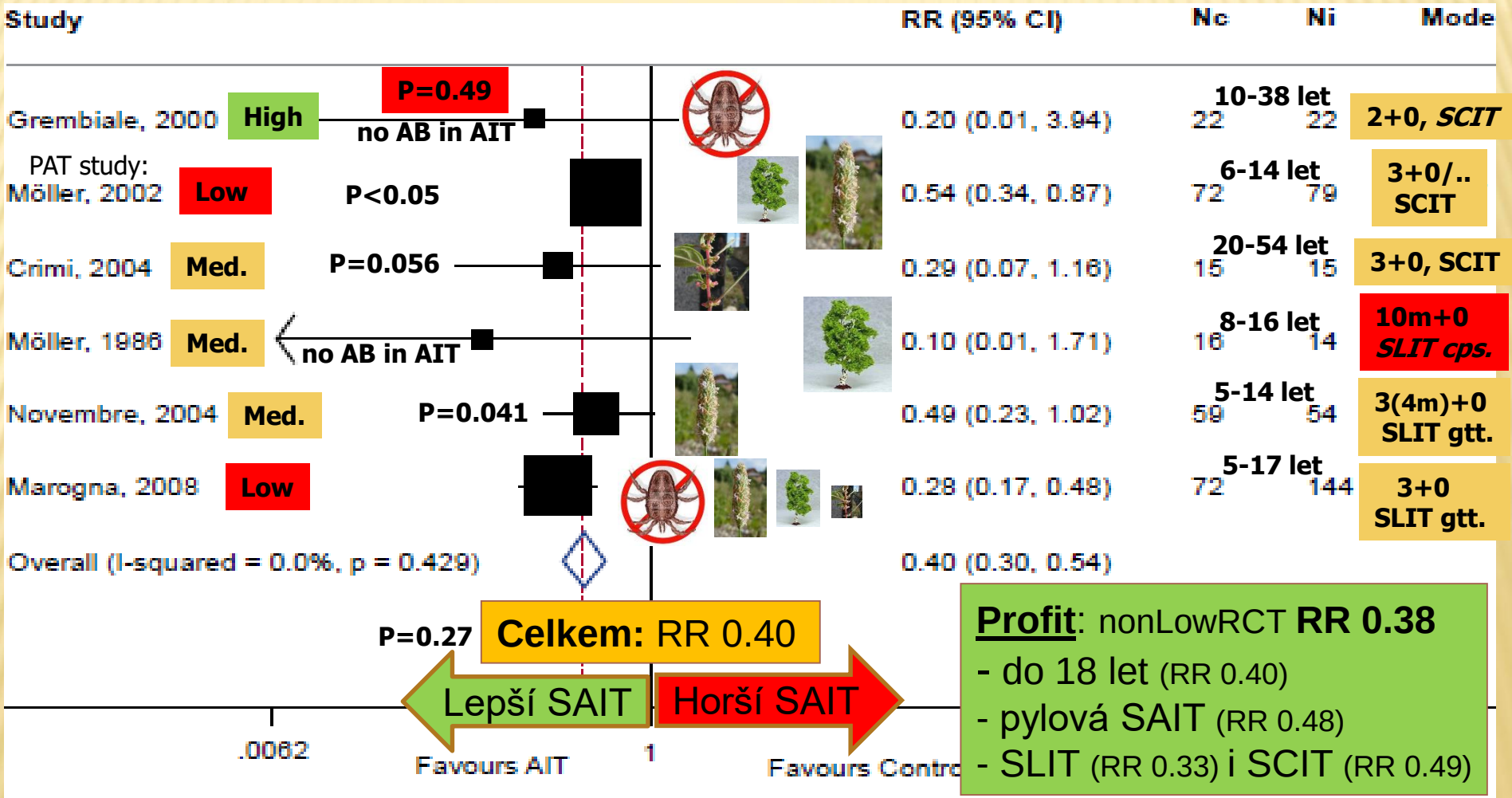


Figure 3 Random-effects meta-analysis of effectiveness of AIT in preventing short-term risk of developing first new allergic disease. Nc = number in control group; Ni = number in intervention group; mode = route of administration of AIT.

SAIT – prevence progrese k AB /RCT/

(krátkodobě tj. v průběhu SAIT a do 2 let po SAIT)



Profit: nonLowRCT **RR 0.38**
- do 18 let (RR 0.40)
- pylová SAIT (RR 0.48)
- SLIT (RR 0.33) i SCIT (RR 0.49)

Figure 4 Random-effects meta-analysis of effectiveness of AIT in short-term prevention of asthma in those with allergic rhinitis. Nc = number in control group; Ni = number in intervention group; mode = route of administration of AIT.

SAIT – prevence progrese k AB /RCT/ (dlouhodobě tj. 2 roky po skončení SAIT a více)

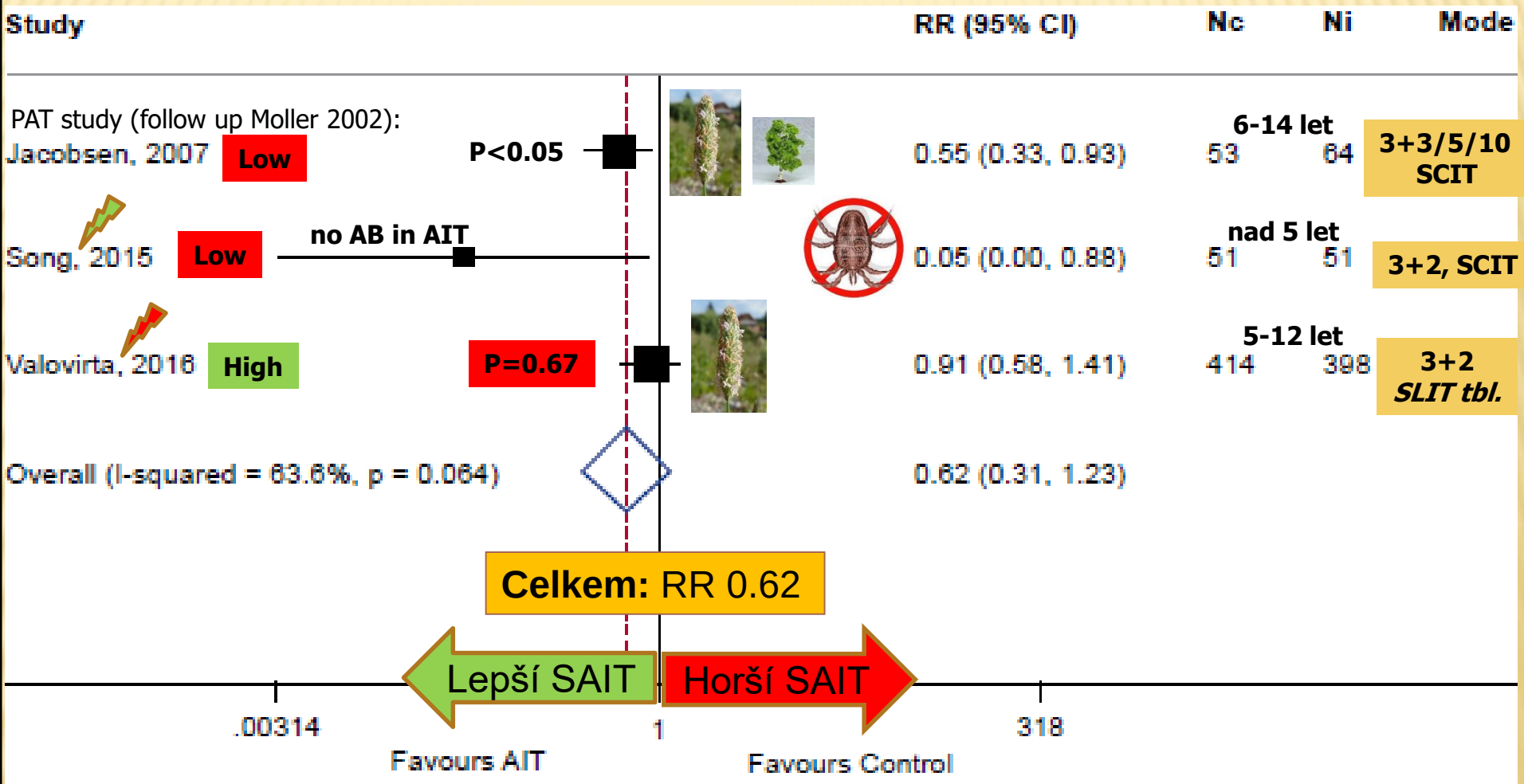
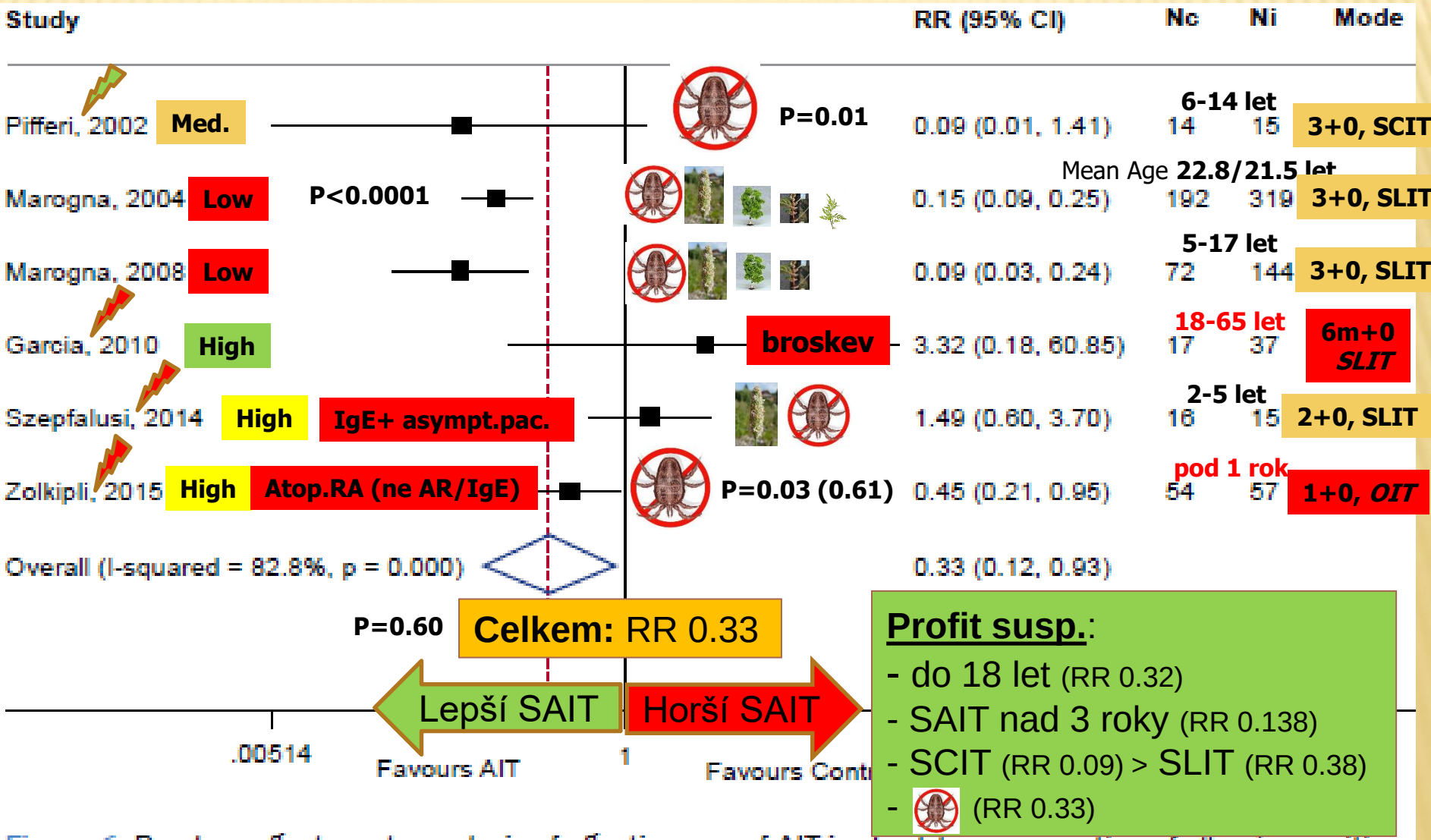


Figure 5 Random-effects meta-analysis of effectiveness of AIT in long-term prevention of asthma in those with allergic rhinitis. Nc = number in control group; vNi = number in intervention group; vmode = route of administration of AIT.

SAIT – prevence spreadingu /RCT/

(krátkodobě tj. v průběhu SAIT a do 2 let po SAIT)



Profit susp.:

- do 18 let (RR 0.32)
- SAIT nad 3 roky (RR 0.138)
- SCIT (RR 0.09) > SLIT (RR 0.38)
- (RR 0.33)

Figure 6 Random-effects meta-analysis of effectiveness of AIT in short-term prevention of allergic sensitization. Nc = number in control group; Ni = number in intervention group; mode = route of administration of AIT.

SAIT – prevence spreadingu /RCT/
(dlouhodobě tj. 2 roky po skončení AIT a více)

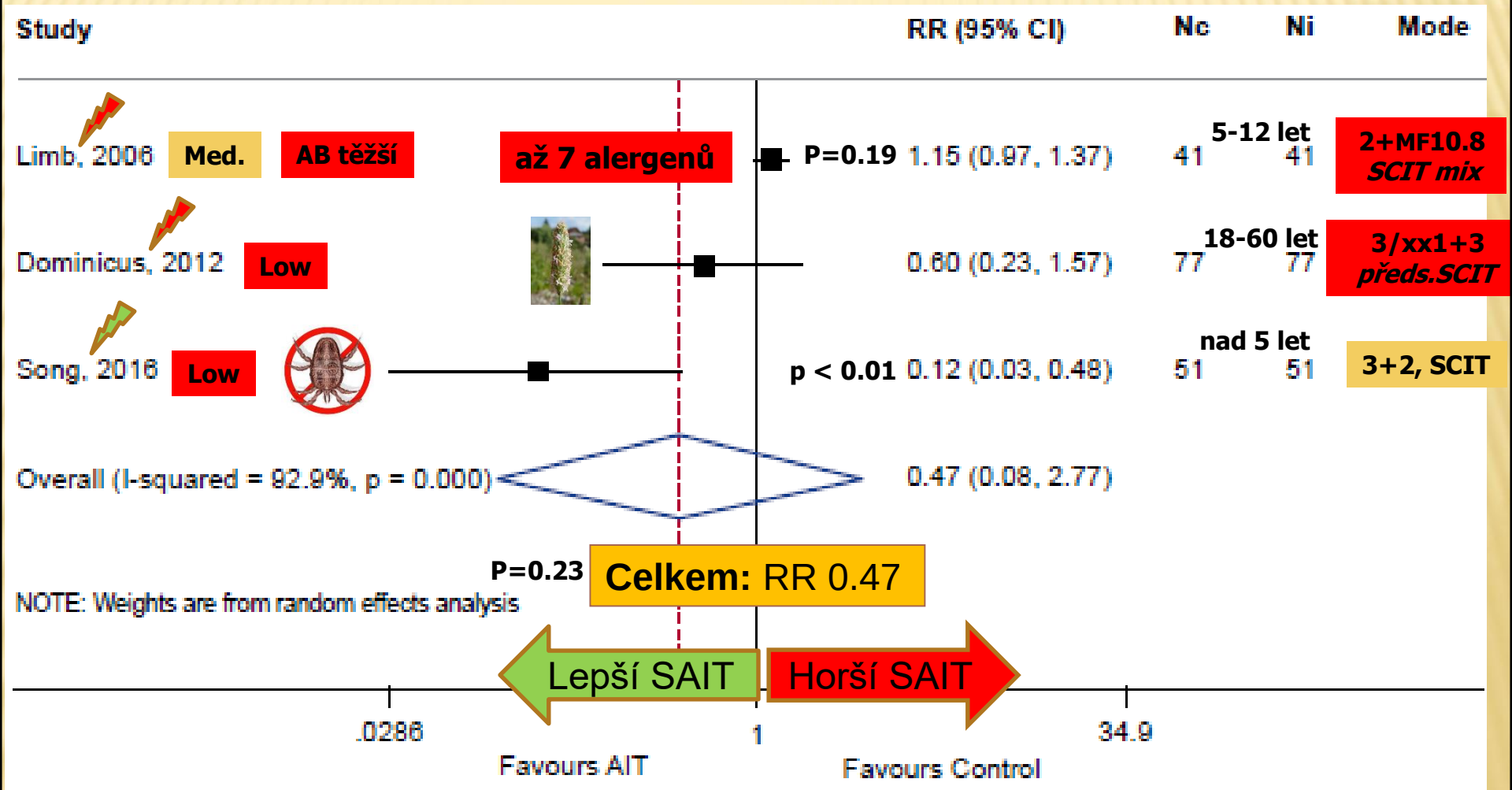


Figure 7 Random-effects meta-analysis of effectiveness of AIT in long-term prevention of allergic sensitization. Nc = number in control group; Ni = number in intervention group; mode = route of administration of AIT.

SAIT – prevence spreadingu /CBA studie, např./

Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study * Purello-D'Ambrosio F. et al. Clin.Exp.All. 2001; 31: 1295-1302.

Retroperspektivní studie – 8396 pacientů (7182 AIT), různé alergeny, AR i AR společně s AB. Léčba AIT 4 roky, posuzováno po 4 (T1) a 7 letech (T2).

	Number of patients	Polysensitized T1 (%)	Polysensitized T2 (%)
SAIT léčba			
Subgroup A1 (rhinitis)	2938	620 (21.10)	702 (23.89)
Subgroup A2 (asthma and rhinitis)	4244	1086 (25.59)	1234 (29.07)
Group A (total)	7182	1706 (23.75)	1936 (26.96)
bez SAIT			
Subgroup B1 (rhinitis)	499	318 (63.72)	356 (71.34)
Subgroup B2 (asthma and rhinitis)	715	508 (71.05)	576 (80.56)
Group B (total)	1214	826 (68.04)	932 (76.77)

SAIT bránila rozvoji polysenzibilizace v čase u AR±AB

(při 4-leté léčbě SAIT bylo po celkem 7 letech /tj. 4+3/ postiženo 27% pacientů SAIT léčených vs. 77% pacientů SAIT NEléčených).

SAIT
kauzální efekty
„budoucí pohled“

SAIT v prevenci alergie – nová data

SAIT – prevence spreadingu (nová metaanalýza)

REVIEW ARTICLE

Efficacy of allergen immunotherapy in reducing the likelihood of developing new allergen sensitizations: a systematic review

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To cite this article: Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Macchia L, Di Lorenzo G. Efficacy of allergen immunotherapy in reducing the likelihood of developing new allergen sensitizations: a systematic review. *Allergy* 2017; **72**: 691–704.

Keywords
allergen immunotherapy; asthma; GRADE; rhinoconjunctivitis; systematic review.

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Accepted for publication 4 December 2016

DOI:10.1111/all.13104

Edited by: Thomas Bieber

Abstract

Background: Guidelines and position papers indicate that allergen immunotherapy (AIT) is the only disease-modifying treatment, including prevention of the onset of new allergen sensitizations. However, this preventive effect was shown by only a few observational studies. Our aim was to systematically review the efficacy of AIT in preventing the onset of new allergen sensitizations.

Methods: Computerized bibliographic searches of Medline, EMBASE, and the Cochrane Library (through June 2015) were supplemented with manual searches of reference lists. Observational studies or randomized controlled trials with a long-term observation period were included. Paired reviewers extracted data about study characteristics and assessed biases. The end point was the risk difference in the onset of new allergen sensitizations between patients treated with AIT and pharmacotherapy. The strength of the evidence was graded based on the risk of bias, consistency, and magnitude of effect, according to the GRADE Working Group's guide.

Results: Eighteen studies (1049 children, 10 057 adults) met the inclusion criteria. The risk of bias was high in all but one study. Low evidence supports the position that AIT prevents the onset of new allergen sensitizations, with 10 of 18 studies reporting a reduction in the onset of new sensitizations in patients treated with AIT *vs* placebo. Small studies and studies with a shorter follow-up showed the highest benefit of AIT.

Conclusions: The overall evidence provides a low-grade level of the evidence supporting the efficacy of AIT in preventing the onset of new allergen sensitizations, but high-quality studies could change this estimate.

Allergen immunotherapy (AIT) has been proven effective, with variable clinical benefit, in reducing symptoms and the use of antisymptomatic medications in patients with allergic rhinoconjunctivitis and asthma (1–3). In contrast to antisymptomatic medications, AIT, administered by the subcutaneous (SCIT) or sublingual (SLIT) route in clinical practice, may have persisting effects after its discontinuation, as it acts through a modification of the immune response. Among these persisting effects, the ability to reduce the likelihood of developing new allergen sensitizations in mono- or polysensitized patients has been shown (2).

The preventive effect of AIT on the onset of new allergen sensitizations was reported in many reviews, position papers, and consensus conference (4–13). However, to support this conclusion the findings from only a few observational studies performed on children and adults were examined in these reports, and an extensive review of the literature has not been conducted, yet (14). Therefore, the primary objective of this study was to evaluate the strength of the evidence of the effect of AIT on prevention of new allergen sensitizations in children and adults. We reviewed the quality of the available studies using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach and the Cochrane Risk of Bias Assessment Tool for Non-randomized and Randomized Studies (15–17).

Di Bona D et al. Efficacy of allergen immunotherapy in reducing the likelihood of developing new allergen sensitizations: a systematic review. Allergy 2017; 72(5): 691_704.

Hodnoceno 18 studií (RCT i CBA, min. 3-letých) tj. 1049 dětí + 10.057 dospělých.

RESUMÉ: prevence spreadingu zaléčením SAIT má málo důkazů !

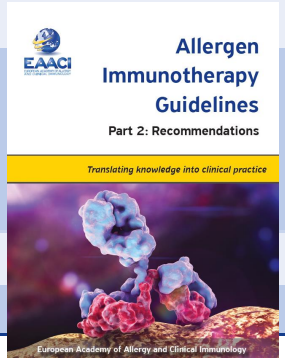
.. 8 z 18 studií neprokázalo vůbec benefit

.. AIT prospěch je jen v malých studích /<100 pac./ a při krátkém follow up /do 3 let/

SAIT v prevenci alergie – potřeba dalších dat

Table 2 Gaps in the evidence

Gaps	Plan to address	Priority
AIT for prevention of asthma in children with AR due to grass pollen - long term effects	Long-term follow up of RCTs Further evaluation of GAP trial	High
AIT for prevention of asthma in children with AR due to HDM	RCTs*	High
Optimal age for introduction of AIT for prevention	RCTs*	High
Optimal duration of AIT for prevention	RCTs*	High
Optimal product, administration form, dose and schedule of AIT for prevention	RCTs* and high quality real life studies	High
Evaluation of influence of AIT for prevention on QoI in different age groups	QoI as outcome in RCTs*	High
AIT for prevention of AR / asthma in children and adults with AD / food allergy	RCTs*	Medium
Evaluation of health economics of AIT for prevention	Cost-effectiveness analysis of RCT	Medium
Evaluation of adherence in AIT for prevention in different age groups	Adherence measured in RCTs and real life studies	Medium
Evaluation of acceptability of AIT for prevention in different age groups	RCTs*	Medium
AIT for the prevention of new allergic sensitizations • spreading from one allergen to related and unrelated allergen(s) • spreading at molecular level, from one allergenic molecule to other molecules	RCTs*	Medium
AIT for prevention of the Oral Allergy Syndrome	RCTs*	Low
AIT for prevention of first allergic disease	RCTs*	Low



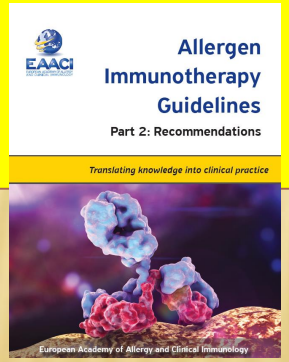
** Apart from new RCTs, published clinical data can be reviewed, raw data can be reanalyzed and blood samples can be analyzed further to provide new data*

SAIT v prevenci alergie – potřeba dalších dat

Je potřeba dalších kvalitních (zejména RCT) studií !!

- **Prevence AB u HDM**
- **Prevence spreadingu**
- **Prevence vzniku alergií**
- **Parametry AIT:**

- optimální věk nasazení
- optimální trvání AIT
- optimální produkty
- optimální dávka
- optimální dávkovací schéma
- ……
- ……
- ……

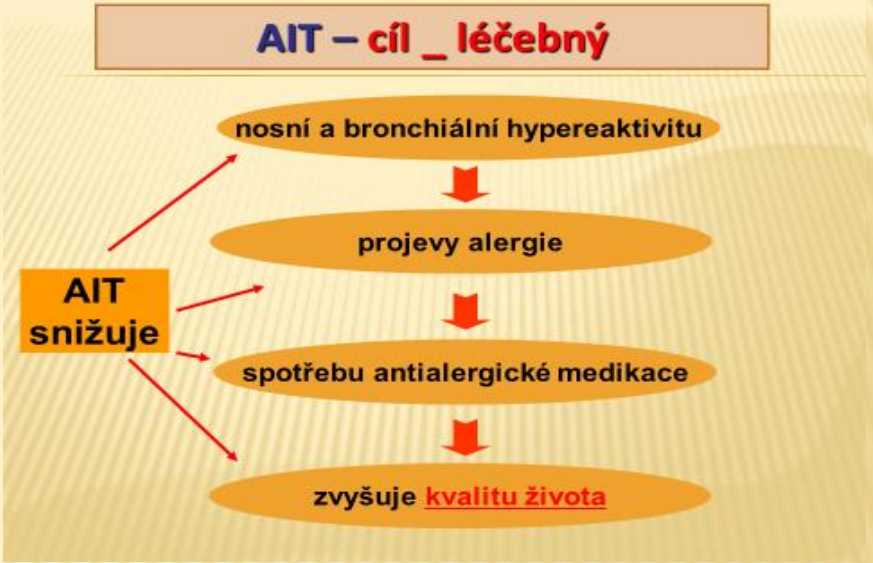


SAIT
kauzální efekty
- osobní pohled

Není třeba propadat pesimismu

SAIT v léčbě alergie

Léčebný cíl



Preventivní cíl

= kauzální efekty léčby

SAIT – cíl léčebný _ efektivita (SLIT traviny)

Metaanalýza studií 2014 (Efekt různých typů léčby pylové alergie)

Symptomatická léčba: 29 publikací
SAIT - SLIT : 10 publikací

21.223 pacientů

Efektivita léčby:	
5 trav SLIT tablety	29,6%
nazální steroidy	23,5%
bojínek SLIT tablety	19,2%
nazální azelastin/flutikazon	17,1%
antihistaminika p.os.	15,0 %
montelukast	6,5%

P.Devillier, JF Dreyfus, P.Demoly, MA Calderón: A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. BMC Medicine 2014, 12:71

SAIT - cíl kauzální _ tradiční východiska

- **SAIT má dlouhotrvající účinnost, efekty SAIT přetrvávají i po jejím ukončení.**

Durham SR. et al. N Engl J Med 1999; 341: 468-75.
Cools M. et al. Allergy 2000; 55:69-73.

- **SAIT chrání před progresí patofyziologického pochodu z alergické rýmy do astmatu.**

Jacobsen L. Allergy 1997;52: 914-20.
Moller C. et al. JACI 2002; 109:251-256.

- **SAIT je prevencí vývoje od monosenzibilizace k alergenové polyvalentní senzibilizaci.**

Des Roches A. et al. JACI 1997; 99:450-53.
Pajno GB. et al. Clin Exp Allergy 2001;31:1392-97.

SAIT
kauzální efekty
- osobní pohled

SAIT zásady pro kauzální efekt ?

- ✓ **dostatečně dlouho (min. 3 roky)**
- ✓ **čím dříve, tím lépe**

SAIT „čím dříve, tím lépe“ – doporučení

WAO

WAO position paper 2013 update

The preventive benefits of AIT may be greater if initiated early in the course of the allergic disease. AIT may alter the natural history of respiratory allergy by preventing the onset of new skin sensitizations and/or reducing the risk of asthma onset.

ICON

ICON - International consensus on allergy immunotherapy 2015

AIT is the only treatment that can change the course of allergic disease by preventing the development of asthma and new allergen sensitizations and by inducing allergen-specific immune tolerance.

CZ

Alergologie - Špičák, Panzner (ed.) Galén/Karolinum 2004

Nejvýhodnější je zahájení AIT v časné fázi alergického onemocnění, neboť AIT klade důraz na prevenci vzniku chronického alergického zánětu, a tím i na prevenci dalšího zánětu, a tím i na prevenci dalšího zhoršování nemoci. (s.133)

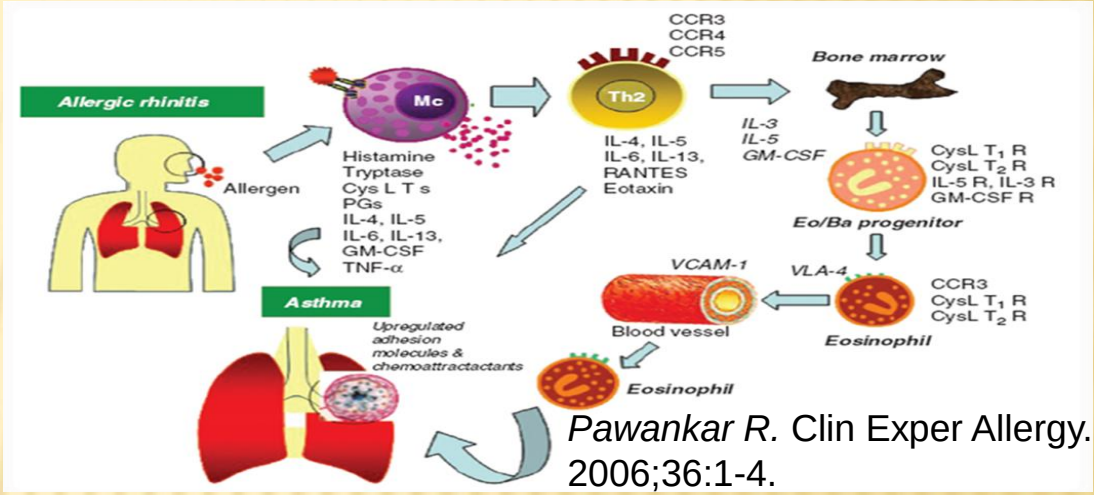
SPC

Souhrn údajů o přípravku - Staloral 300, 2017

(CZ) 4.2 Dávkování a způsob podání: Je třeba uvážit výhody časného zahájení alergenové imunoterapie při rozvoji onemocnění.

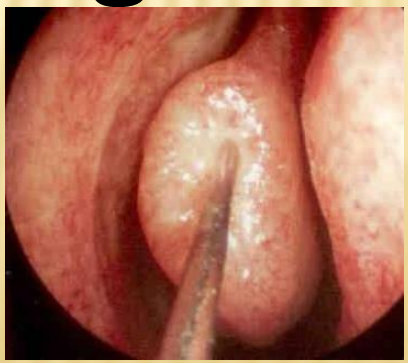
SAIT „čím dříve, tím lépe“ – klinické terap.okno

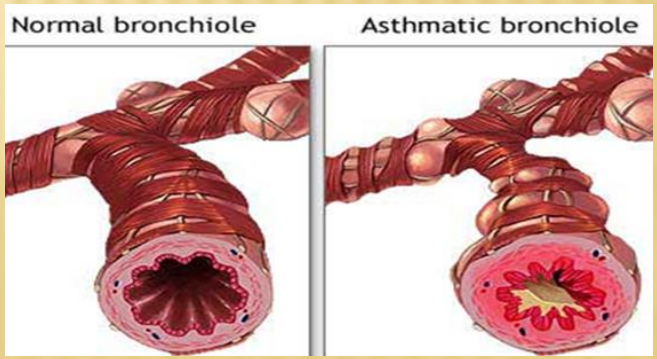
Úroveň (sub)buněčná



Pawankar R. Clin Exper Allergy. 2006;36:1-4.

Úroveň orgánová a tkáňová





SAIT „čím dříve, tím lépe“ – klinické terap.okno

Monosenzibilizace

a slabá IgE odpověď

SAIT produkty - indikace:

.. kumulativní dávka (monovalentní terapie)

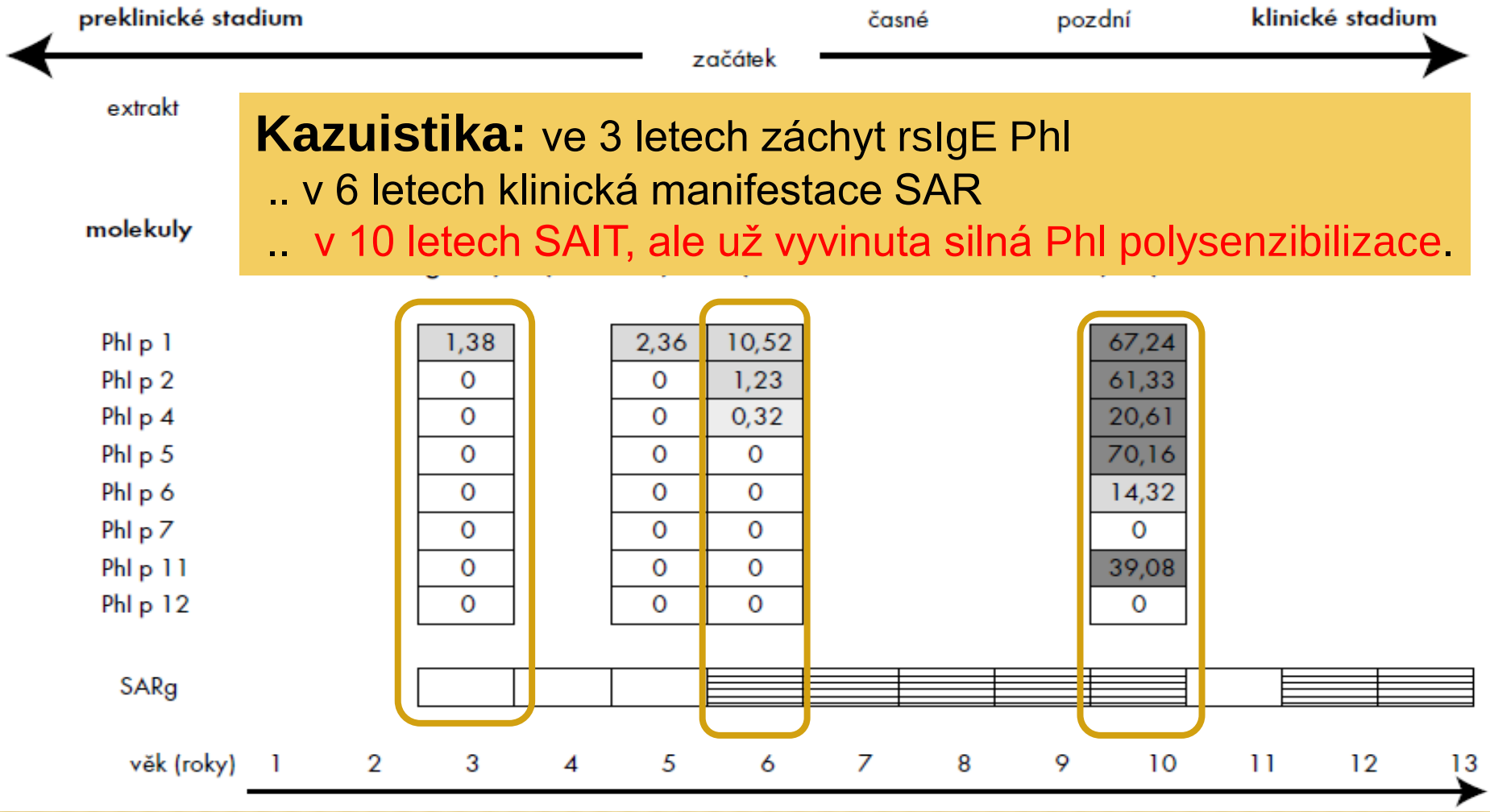
.. standardizace produktu (hlavní alergeny)

Polysenzibilizace

a silná IgE odpověď

SAIT „čím dříve, tím lépe“ – klinické terap.okno

Matricardi PM. *Třídění IgE-odpovědí do skupin podle molekulárních profilů a jeho možné důsledky pro specifickou imunoterapii.* Curr Opin Allergy Clin Imun/CS (2014)



SAIT

je KAUZÁLNÍ terapie

a stále počítám s jejími preventivními účinky

Děkuji za pozornost ☺