Interventions for melasma

Overview

- Melasma – who what where why?
- Evidence for what treatments work- Cochrane review
- New key trials
- My practice and pitfalls

Overview

- Melasma – who what when where why?
- Evidence for what treatments work- Cochrane review
- New key trials
- My practice and pitfalls

Overview

- Melasma – who what where why?
- Evidence for what treatments work- Cochrane review
- New key trials
- My practice and pitfalls

Systematic review of randomized controlled trials on interventions for melasma: an abridged Cochrane review. J Am Acad Dermatol 2014 Feb;70(2): 369-73

Overview

- Melasma – who what where why?
- Evidence for what treatments work- Cochrane review
- New key trials
- My practice and pitfalls

Overview

- Melasma – who what where why?
- Evidence for what treatments work- Cochrane review
- New key trials
- My practice and pitfalls

What is Melasma ?

- Acquired, chronic recurrent hyperpigmentation of the skin

- Characterised by symmetrical light to dark muddy brown macules and patches mostly on the areas of the face exposed to the sun, such as the cheek bones, forehead, and chin

Who is affected ?

- More common in women
- Prevalence of melasma ranges from 8.8% in Latino females in Southern US to as high as 40% in Southeast Asian populations.
- A survey of 2000 Afro Carribean participants in Washington found melasma to be the third most common pigmentary disorder of the skin
- A multicenter survey of females from 9 countries found that Fitzpatrick skin phototypes III and IV were most commonly affected.

Why melasma occurs ?

- UV light, is commonly reported initiating or exacerbating factor. Patients report increased severity of melasma with sun exposure.
- Genetic predisposition -high reported incidence in family members in several studies but the exact risk is unknown.
- Hormonal link to melasma- Many patients note onset or worsening with pregnancy or oral contraceptives. Studies report 5-50% of patients identified pregnancy as a triggering factor.
- Thyroid disorders and stress

Overview

- ✓ Melasma – who what where why?
- ✓ Evidence for what treatments work- Cochrane systematic review
- ✓ New key trials
- ✓ My practice and pitfalls

Interventions for melasma

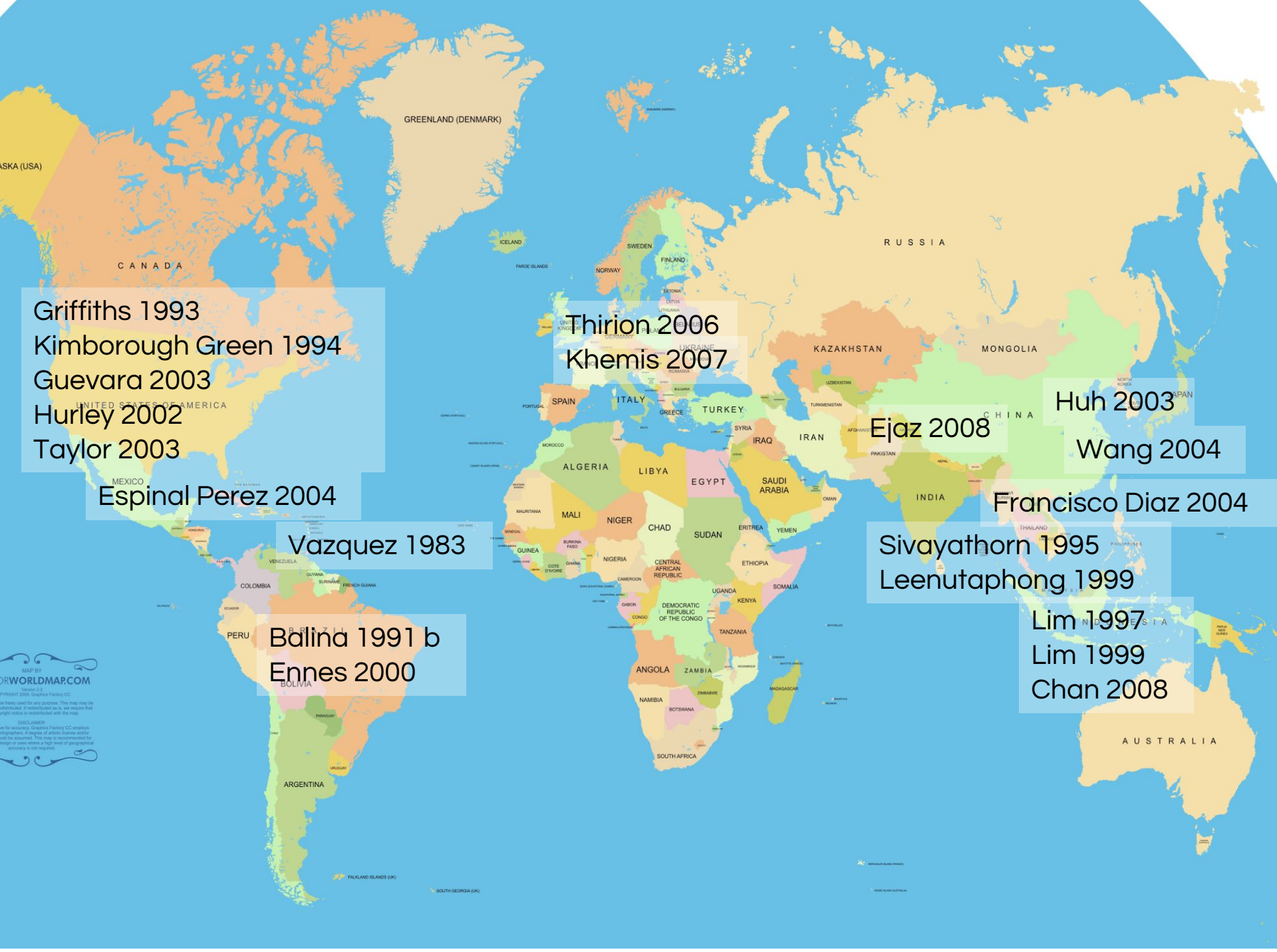
- Assess treatments to limit or reduce melasma and prevent recurrence

- No language restriction
- Published and unpublished RCTs relating to the treatment of melasma
- Open label trials (placebo use possible) were included if assessment was done blindly
- Open label trials (placebo use not possible) included if assessment was done blindly OR objective measures used
- Patient assessed change in melasma severity and QOL
- Physician assessed change, Side effects

Summary findings

- Included 20 studies
- 2125 participants
- 23 different treatments

- Bleaching agent eg hydroquinone (8)- Balina 1991b, Chan 2008, Ennes 2000 Espinal Perez 2004, Hurley 2002, Vazquez 1983, Wang 2004; Sivayathorn 1995
- Azelaic acid (2) -Balina 1991b; Sivayathorn 1995
- Topical retinoid (3)-Griffiths 1993; Kimborough-Green 1994, Leenutaphong 1999
- Combination creams (6)- Espinal Perez 2004; Chan 2008; Taylor 2003; Guevara 2003; Lim 1997;Lim 1999
- Combination therapies (4)-Hurley 2002; Lim 1997; Wang 2004; Ejaz 2008
- Less conventional therapies(4)- Khemis 2007; Huh 2003; Thirion 2006; Franscisco Diaz 2004


Griffiths 1993
Kimborough Green 1994
Guevara 2003
Hurley 2002
Taylor 2003
Espinal Perez 2004
Vazquez 1983
Balina 1991 b
Ennes 2000
Thirion 2006
Khemis 2007
Ejaz 2008
Huh 2003
Wang 2004
Francisco Diaz 2004
Sivayathorn 1995
Leenutaphong 1999
Lim 1997
Lim 1999
Chan 2008
GREENLAND (DENMARK)
CANADA
RUSSIA
UNITED STATES OF AMERICA
MEXICO
BRAZIL
ARGENTINA
PERU
COLOMBIA
BOLIVIA
CHINA
INDIA
AUSTRALIA
KAZAKHSTAN
MONGOLIA
SAUDI ARABIA
IRAN
IRAQ
SYRIA
TURKEY
ALGERIA
LIBYA
EGYPT
SUDAN
CHAD
NIGER
MALI
NIGERIA
ETHIOPIA
SOMALIA
KENYA
TANZANIA
ANGOLA
ZAMBIA
NAMIBIA
BOTSWANA
SOUTH AFRICA
DEMOCRATIC REPUBLIC OF THE CONGO
CENTRAL AFRICAN REPUBLIC
SPAIN
ITALY
GREECE
SWEDEN
FINLAND
NORWAY
ICELAND
UKRAINE
GERMANY
PAKISTAN
INDONESIA

Summary findings

- Included 20 studies
- 2125 participants
- 23 different treatments

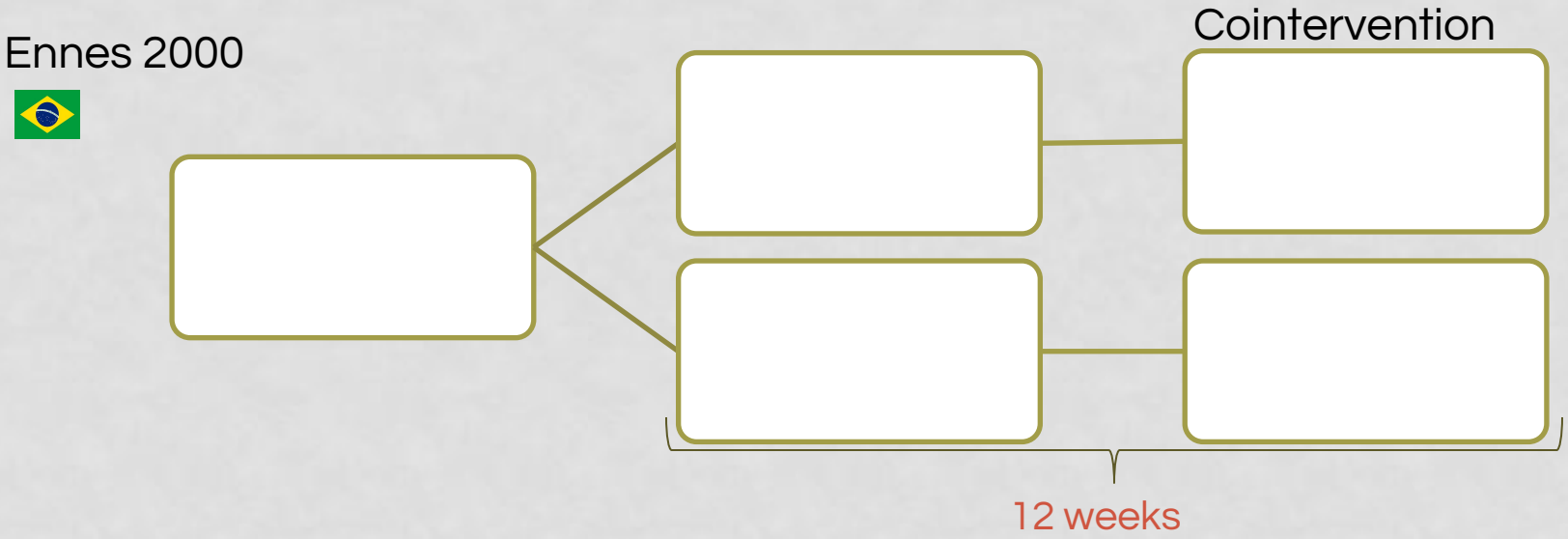
- **Bleaching agent eg hydroquinone** (8)- Balina 1991b, Chan 2008, Ennes 2000 , Espinal Perez 2004, Hurley 2002, Vazquez 1983, Wang 2004; Sivayathorn 1995
- Azelaic acid (2) -Balina 1991b; Sivayathorn 1995
- Topical retinoid (3)-Griffiths 1993; Kimborough-Green 1994, Leenutaphong 1999
- Combination creams (6)- Espinal Perez 2004; Chan 2008; Taylor 2003; Guevara 2003; Lim 1997;Lim 1999
- Combination therapies (4)-Hurley 2002; Lim 1997; Wang 2004; Ejaz 2008
- Less conventional therapies(4)- Khemis 2007; Huh 2003; Thirion 2006; Franscisco Diaz 2004

WHAT FORMULATION OF HYDROQUINONE TO USE?

What formulation of hydroquinone to use?

- The formulation of hydroquinone used was mostly 4% hydroquinone cream
- All trials using hydroquinone compared 2 active interventions.

Evidence for 4% Hydroquinone



- Physicians assessed improvement according to one of three categories: total improvement, partial improvement, or failure.

Physician subjective evaluation of improvement

	4% HQ + sunscreen	Sunscreen only
Total improvement	8	2
Partial improvement	12	14
Failure	0	4
Total	20	20

*Outcomes were not reported in 5 participants

- Statistically significant difference between the groups in favour of HQ and sunscreen. (authors report P = 0.0082-unclear which category of improvement analysed)
- This significant difference between the groups evident from week 3.
- No difference in tolerability. Adverse events eg. mild erythema(RR 1.37, 95% CI 0.49 to 3.85). No serious adverse events

4% Hydroquinone - Conclusion

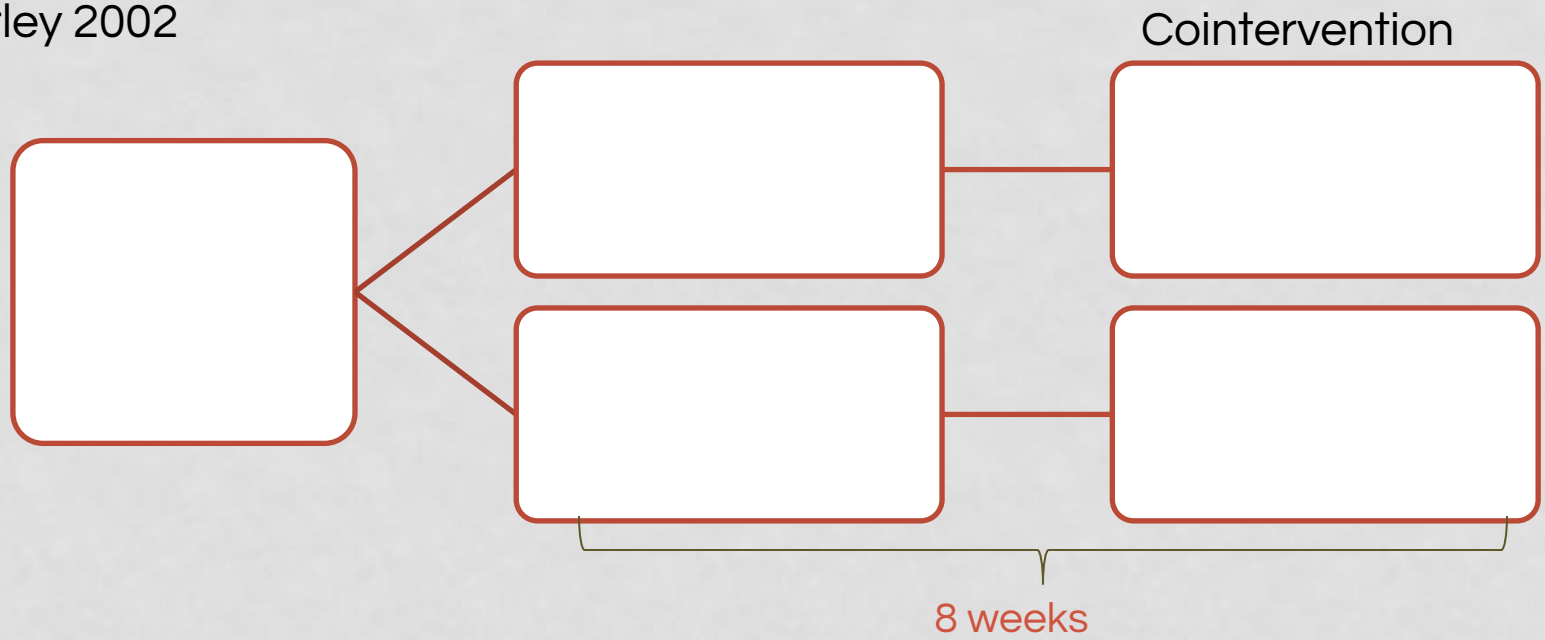
- Hydroquinone 4% is a safe and effective for the treatment of melasma and that sunscreens are important as concomitant treatment by way of preventing repigmentation.

- One outcome measure and incomplete
- well tolerated
- early onset of action- week 3

WOULD COMBINING HYDROQUINONE WITH ANOTHER TREATMENT BE MORE EFFECTIVE?

Evidence for 4% Hydroquinone + Peels

Hurley 2002



- 11/18 participants felt there was more improvement on the peeled side versus 4/18 on the non-peeled side. One of the 18 felt there was no difference between the 2 sides.

- Missing data on two participants

Evidence for 4% Hydroquinone + Peels

- On the physician evaluation, there was a significant improvement from baseline in both groups there was no significant difference between the sides in terms of objective mexameter reading or subjective MASI scores.

- Four participants developed significant erythema though no peeling or erosions occurred secondary to the peels.

4% Hydroquinone + Peels- Conclusion

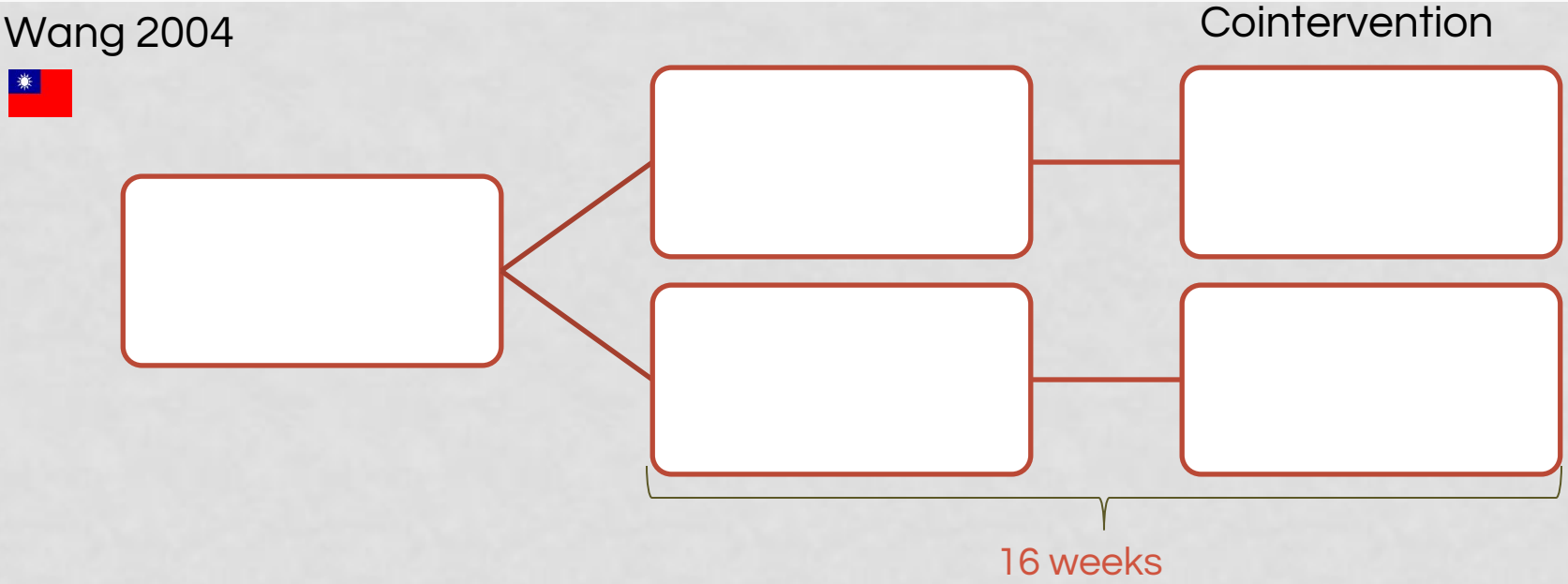
- Authors concluded that 4% hydroquinone is effective in the treatment of melasma but the addition of 4 glycolic acid peels did not enhance the effect of hydroquinone.

-Incomplete data on participant outcomes

-Sponsored by ICN pharmaceuticals manufacture peels and creams

Evidence for 4% HQ + Intense Pulse Light

Wang 2004



- The frequency of hydroquinone application in either group is unclear.
- The rationale for hydroquinone in the control arm where participants had been shown to be unresponsive is also unclear.

Participant subjective evaluation of improvement

	4% HQ	4% HQ + IPL
Satisfied	0	23.5%
Slightly satisfied	64%	53%
Unsatisfied	36%	23.5%
Total no. participants	17	14

- On objective measures, there was a greater reduction in the melanin index score in the hydroquinone and pulsed light group ((39.8% in HQ+IPL versus HQ group 11.6% authors report $P < 0.05$).

- Adverse events were noted in the IPL group- mild erythema and pain, microcrust for 1-2 weeks, 2 patients with PIH settled with HQ.

4% HQ + Intense Pulse Light- Conclusion

- Authors concluded that IPL is safe and effective treatment for refractory melasma with minimal side effects.

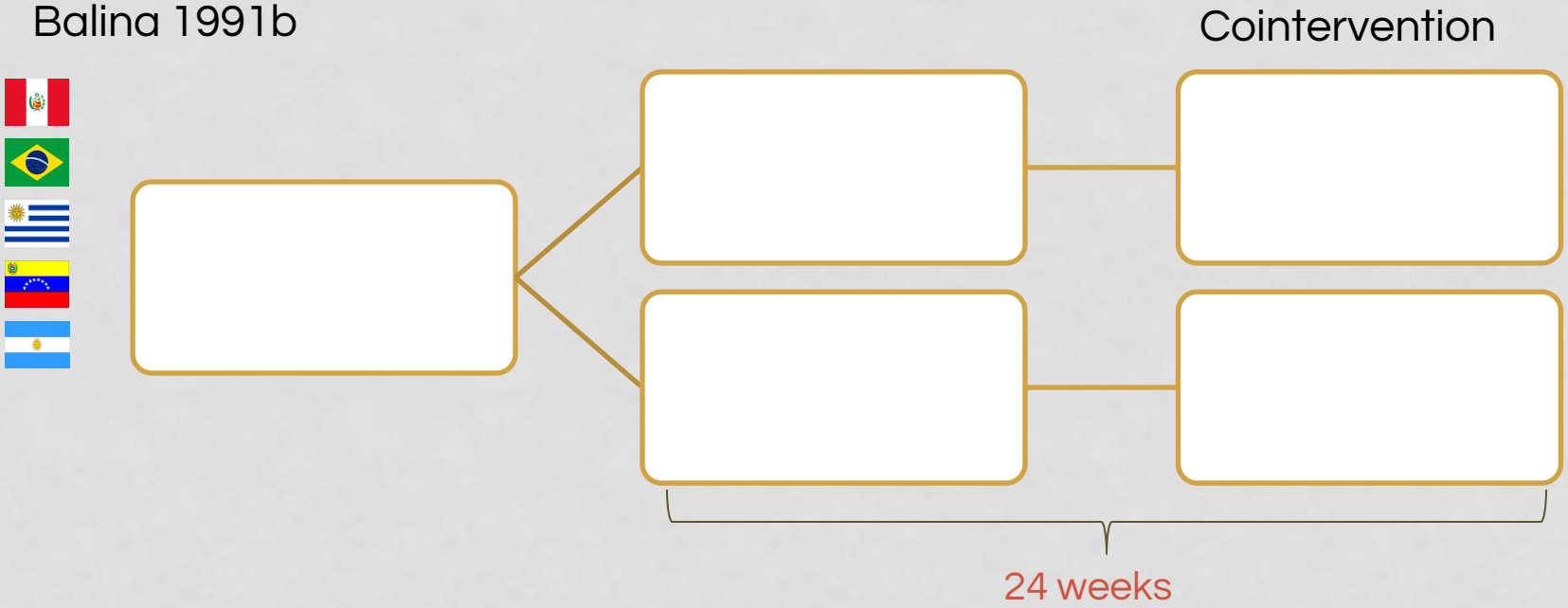
-No frequency of HQ and if same between groups

-2/17 post inflammatory hyperpigmentation in the IPL group

ARE THERE ALTERNATIVES AT LEAST AS EFFECTIVE HYDROQUINONE?

20% Azelaic acid vs 4% Hydroquinone

Balina 1991b



- There was a large loss to follow up (86 participants). Differential loss to follow up not significant. Assessments performed on 122 participants in the azelaic acid and 121 participants in the hydroquinone group.

20% Azelaic acid vs 4% Hydroquinone

- Physicians rated 71.9% of those in the hydroquinone group as good/excellent response versus 64.8% in the azelaic acid group (RR 1.11, 95% CI 0.94 to 1.32;).
- On the objective measure of reduction in lesion size, no significant difference was demonstrated.
- Side-effects (local irritation) were mild occurring more frequently in the azelaic acid group (18/122) versus the hydroquinone group (1/121 allergic sensitisation) (RR 17.85, CI 2.42 to 131.64;)

20% Azelaic acid vs 4% HQ-Conclusion

- No significant differences between 20% azelaic acid and 4% HQ. Severe side effects did not occur with azelaic acid.

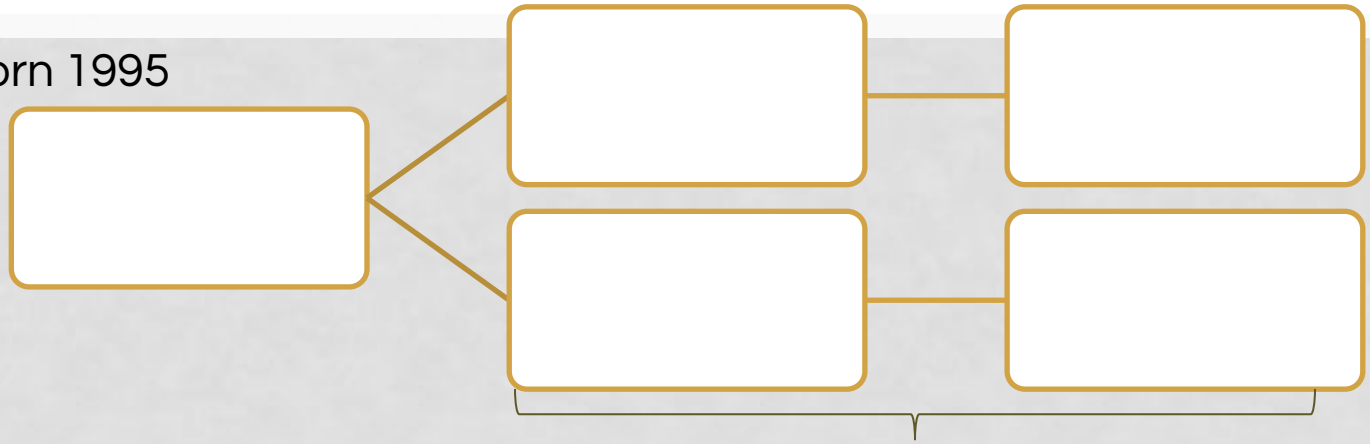
-Large loss to follow up (26%)

-Local irritation in 18/122 azelaic acid

-Sponsored by Schering AG, Berlin- unclear if they manufacture study creams

20% Azelaic acid vs 2% Hydroquinone

Sivayathorn 1995



- Physicians rated significantly more participants in the azelaic acid group (75.5%) as having a good/excellent response compared to 2% HQ group(47.1%).
- No statistically significant difference between the groups on objective measure of reduction in lesion size.
- Itching, burning, and erythema in 76/147 in the azelaic acid group and 24/153 in the HQ group. (RR 3.3, 95% CI 2.21 to 4.91)

20% Azelaic acid vs 2% HQ-Conclusion

- 20% Azelaic more effective than 2% HQ on some measures comparable on others.

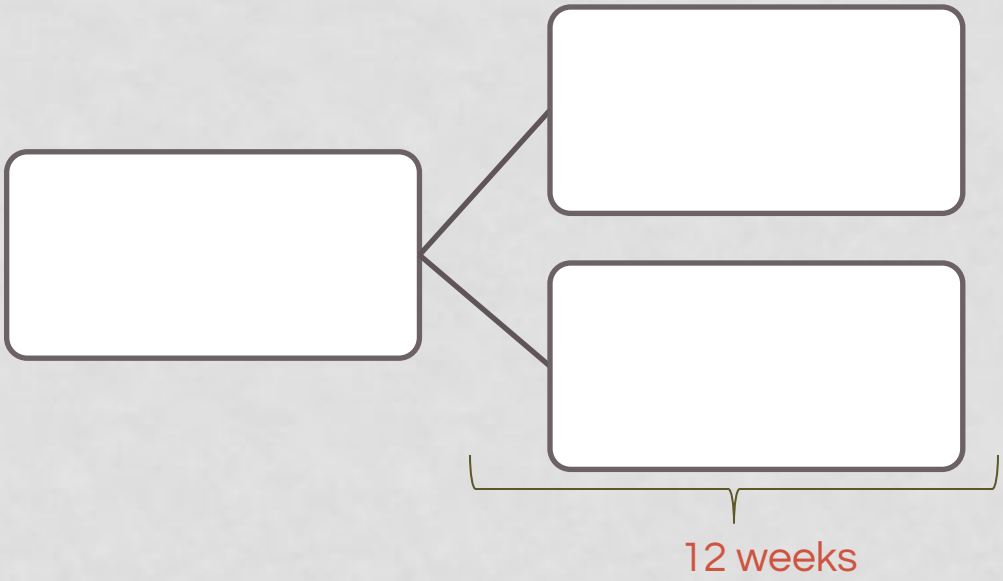
- Confirms the side effect profile of Azelaic acid, irritation in 76/153 vs 23/153

-Lower strength of HQ may be less effective

ARE THERE ANY TOPICALS MORE EFFECTIVE THAN HQ?

Evidence for Hydroquinone + Sunscreen

Vazquez 1983



- The physicians rated a higher proportion of participants in the hydroquinone and sunscreen group (96.3%) as improved compared to the hydroquinone-only group (80.8%).

Participant subjective evaluation of improvement

	3% HQ + sunscreen	3% HQ
Marked improvement	8	7
Moderate improvement	14	14
Slight improvement	5	4
Worse	0	1
Total	27	26

- 9 participants [illegible] clear which arm.

3% Hydroquinone + Sunscreen- Conclusion

- Although no statistical analysis was conducted, the trial authors concluded that hydroquinone is the main stay of therapy and addition of a sunscreen has a positive effect.

-Only study to evaluate the effect of sunscreen on melasma

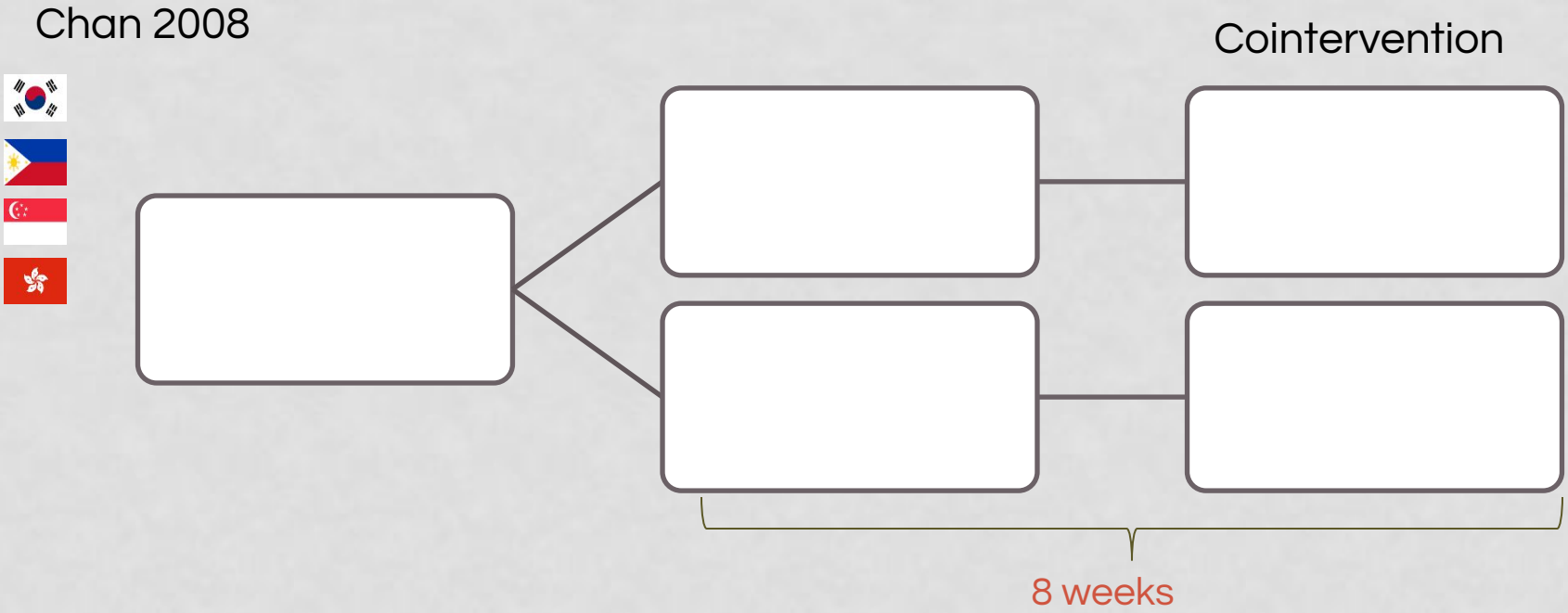
-Incomplete data eg 6 patients loss to fu- unsure which group

-Neutrogena and Herbert laboratories supplied study creams

Triple combination cream

(fluocinolone acetonide 0.01%, HQ 4%, tretinoin 0.05%) vs 4% HQ

Chan 2008



- On participant reported outcomes, significantly more participants (71%) in the triple-combination group versus 50% in the hydroquinone group were satisfied or very satisfied (trial authors report P = 0.005).

Triple combination cream vs 4% HQ

- This significant difference was also reflected in the physician assessment. More participants in the TC group achieved score of 0 (none) or 1(mild) on melasma severity scale. Authors stated $P < 0.001$.

- Early onset of action with significant differences in the score evident at week 4.

- More patients had related adverse events on TC (63/129, 48.8%) than on HQ (18/131, 13.7%) but most were mild (erythema, irritation and discomfort) and none severe.

Triple combination cream vs 4% HQ- Conclusion

- Efficacy in Asians and patient satisfaction were superior with TC than with HQ 4%

-Patient satisfaction assessed

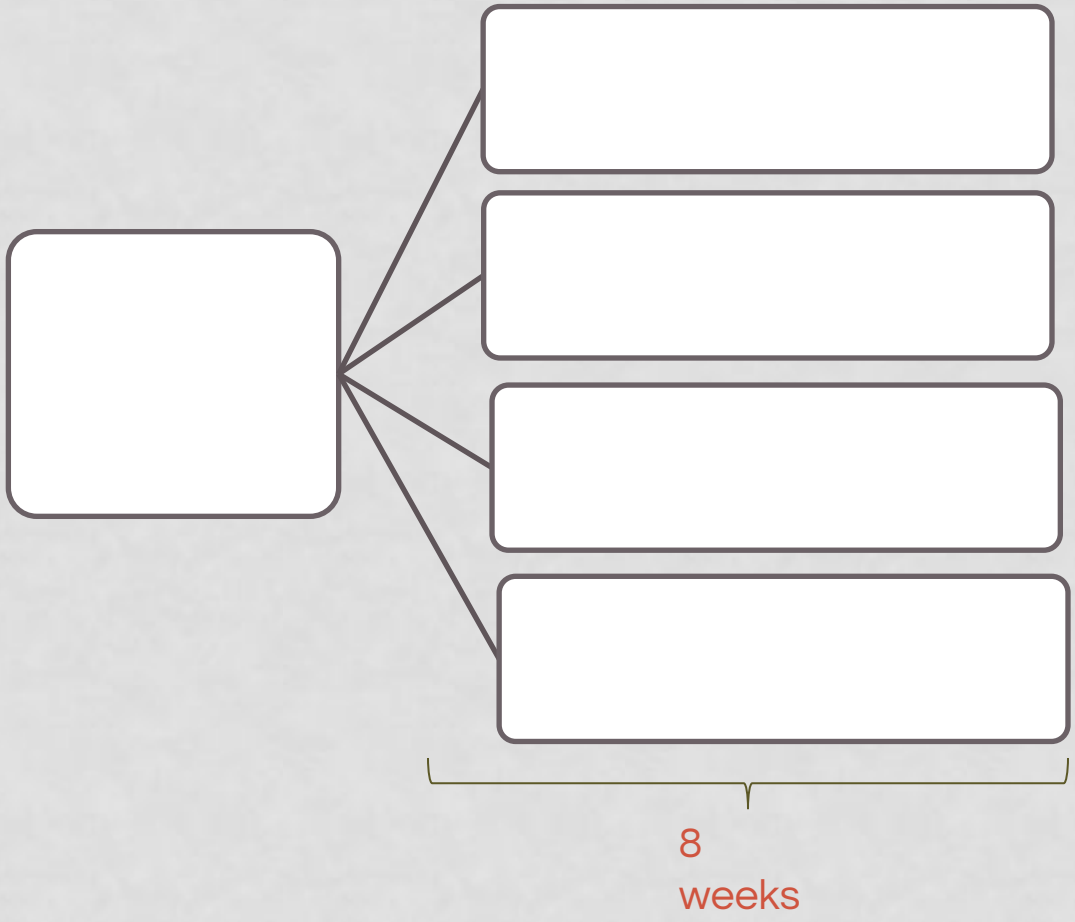
-Early onset of action, though half of patients had side effects (48.8% versus 13.7%)

-Sponsored by Galderma manufacture TCC, 2 authors employees of Galderma

DO YOU NEED ALL THREE INGREDIENTS IN TRIPLE COMBINATION CREAM?

Triple combination cream vs Dual combination agents

Taylor 2003



Triple combination cream vs Dual combination agents- Conclusion

- Triple combination was significantly more efficacious compared to each dual combinations on physician subjective evaluation

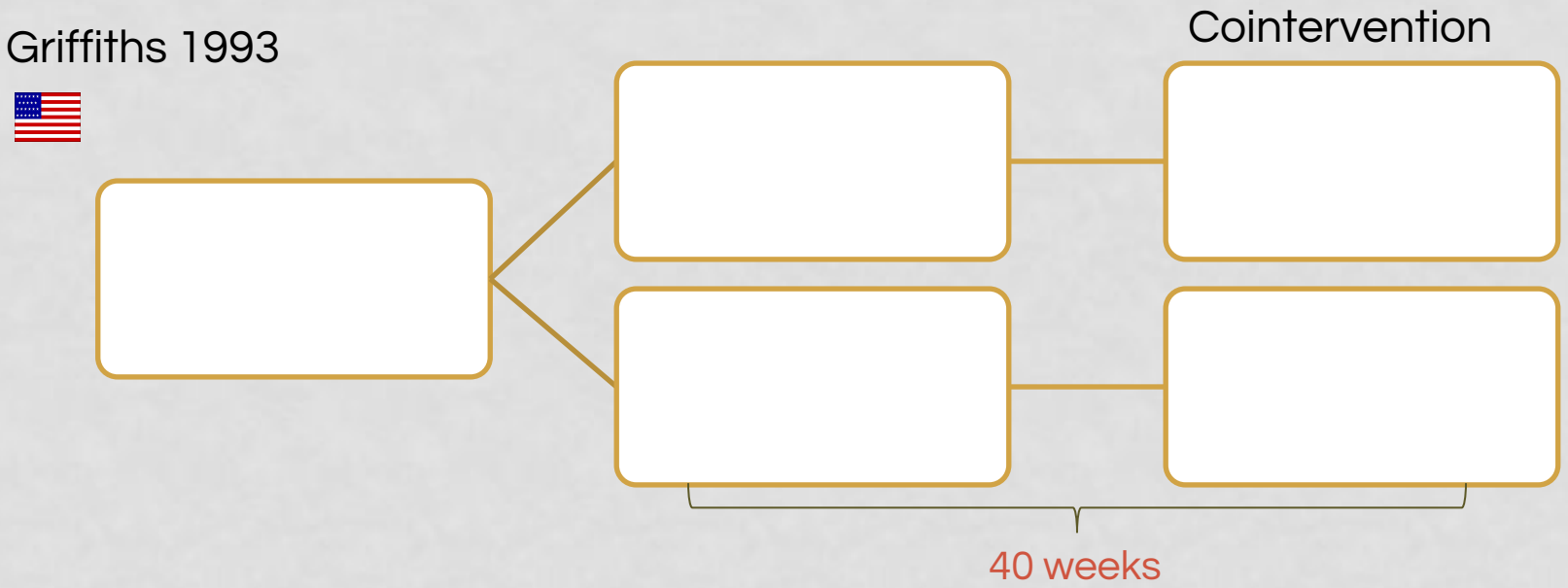
-Study design was complex- Pooled data ? Homogenous

-Confirms that side effect profile of TC seen in 63% (erythema, desquamation, burning)

-Sponsored by Galderma

ARE THERE ANY OTHER ALTERNATIVE TREATMENTS?

Evidence for 0.1% Tretinoin cream



- 94% epidermal, 4% dermal, and 2% mixed melasma.
- At 40 weeks there was significant difference favouring tretinoin on physician assessed subjective measures and objectively with colorimetry.

Evidence for 0.1% Tretinoin cream

- The onset of improvement is slow. First significant improvement occurred at 24 weeks of tretinoin treatment.

- Moderate redness and peeling noted in 22/25 tretinoin participants. In a further five tretinoin participants the reaction was severe.

0.1% Tretinoin cream- Conclusion

- Topical 0.1% tretinoin produces significant clinical improvement of melasma, mainly due to reduction in epidermal pigment, but improvement is slow.

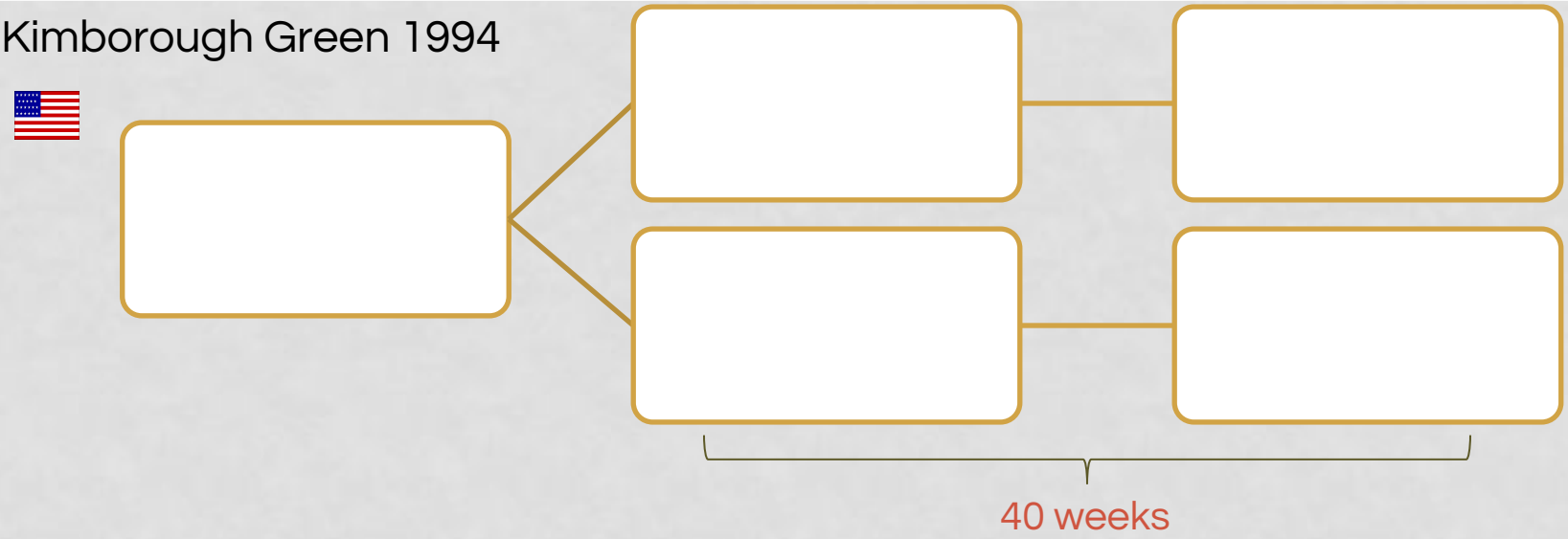
-Study with longest duration.

-Numbers of side effects confusing nonetheless moderate /severe side effects in all patients

-WJohnson Pharmaceutical research institute, NJ but no part in design or conduct of study and Babcock dermatologic endowment, michigan, USA

2. Evidence for 0.1% Tretinoin cream

Kimborough Green 1994



- 43% epidermal, 37% dermal, and 20% mixed melasma.
- 2 subjective measures. No significant difference on the scale of much worse to much improved, there was significant difference in mean reduction of MASI score (32% in tretinoin group vs placebo 10%, P = 0.03).
- The significant improvement was also confirmed on colorimetry (the trial authors report P = 0.02).

0.1% Tretinoin cream- Conclusion 2

- More adverse events in tretinoin group with mild erythema and/or peeling in 10/15 participants versus 1/15 in the placebo group (RR 10.0, 95% CI 1.46 to 68.69).

-Long duration. Efficacy in dermal melasma. (some not all measures)

-Confirms side effects

-RWJohnson Pharmaceutical research institute but no part in design or conduct of study and Babcock dermatologic endowment, michigan, USA

Omissions

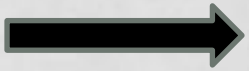
- Less conventional therapies- Rucinol serum, Vitamin C iontophoresis, Thiospot, Gigawhite

- Combination creams-
- HQ+Glycolic acid+ Vit C+ Vit E+ sunscreen
- HQ+ Glycolic acid+ kojic acid
- HQ+Glycolic acid

- Isotretinoin gel
- Jessners peel/ Salicyclic acid peel
- 5% L ascorbic acid

Overview

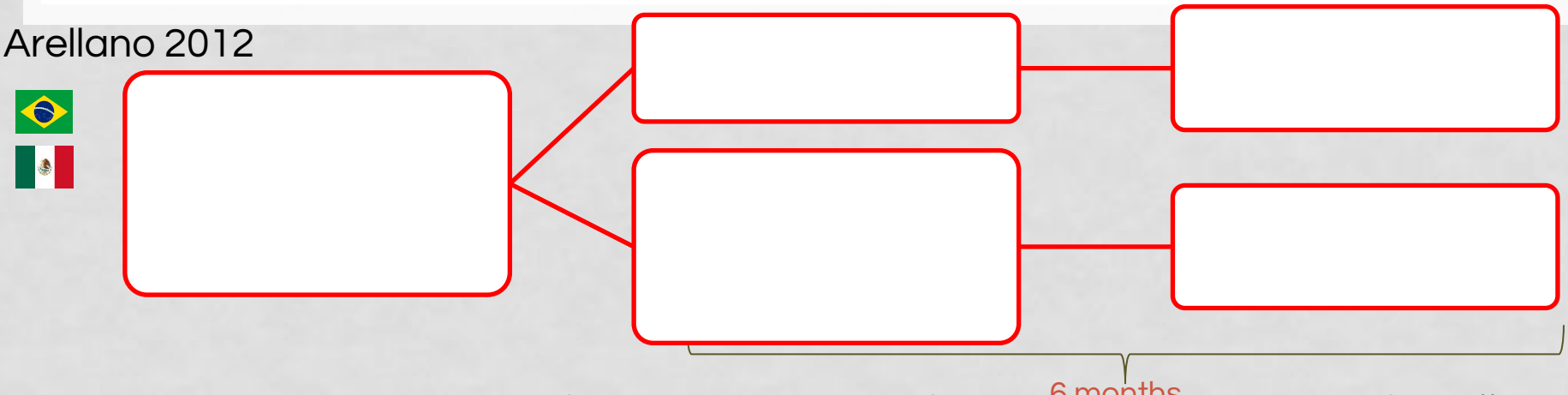
- ✓ Melasma – who what where why?
- ✓ Evidence for what treatments work- Cochrane systematic review
- ✓ New key trials
- ✓ My practice and pitfalls



Preventing melasma recurrence

New trials- preventing melasma recurrence

Arellano 2012

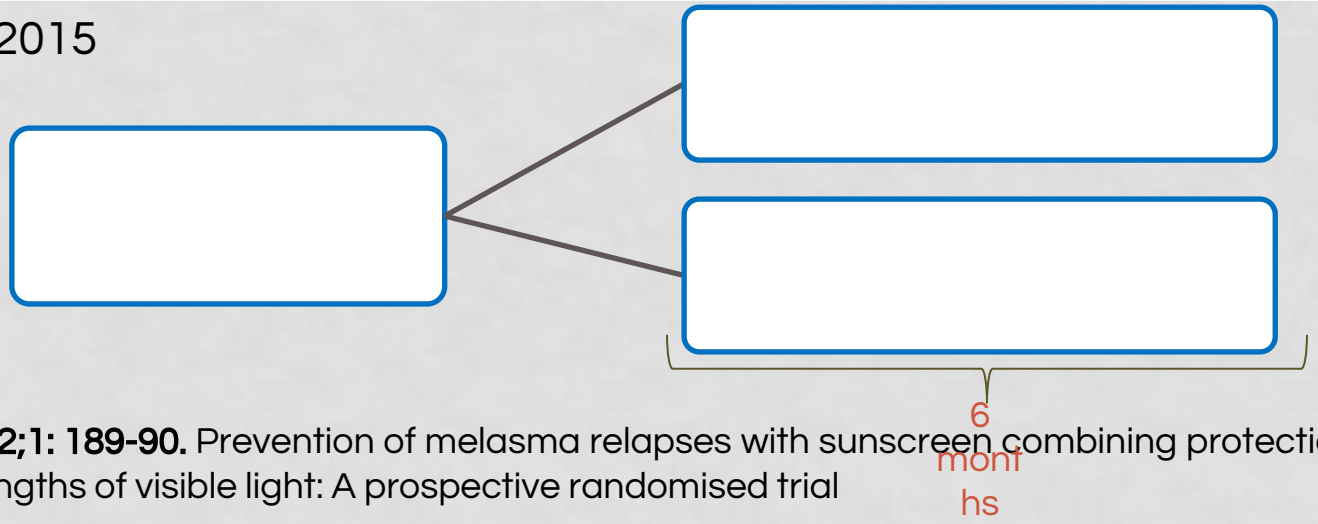


2012 JEADV 26;611-8. Preventing melasma recurrence: prescribing a maintenance regimen with an effective triple combination cream based on long standing clinical severity

- In both arms 53% remained relapse free (53.8% in twice weekly vs 53% in tapering regimen). Time to relapse was similar in both groups (mean 190 days)
- Side effects (redness and irritation) 10.9% in tapering vs 12.2% in twice weekly. 1 patient had atrophy in the twice weekly group, 6 telangectasia
- After resolution of melasma, maintenance therapy over 6 months could prevent recurrence in over half of patients

New trials- preventing melasma recurrence

Boukari 2015



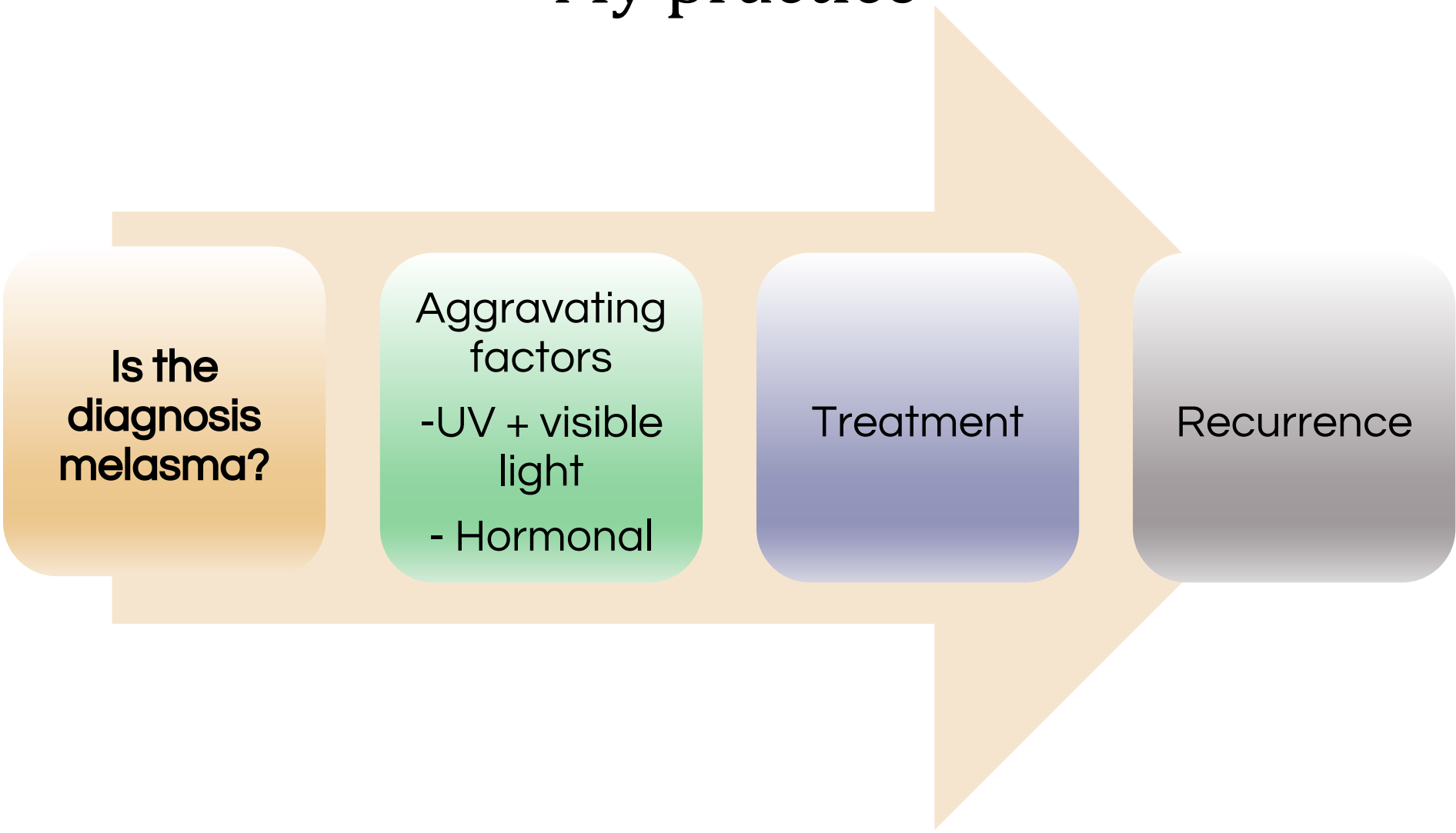
2015 JAAD 72;1: 189-90. Prevention of melasma relapses with sunscreen combining protection against UV and short wavelengths of visible light: A prospective randomised trial

- No information on previous treatment. Primary outcome- MASI
- The median increase in MASI from baseline to month 6 was significantly higher with formula B (no visible light protection) compared to formula A (P=0.027)
- Sunscreen with UVA/UVB and visible light filters are more protective against relapses than sunscreen without visible light protection

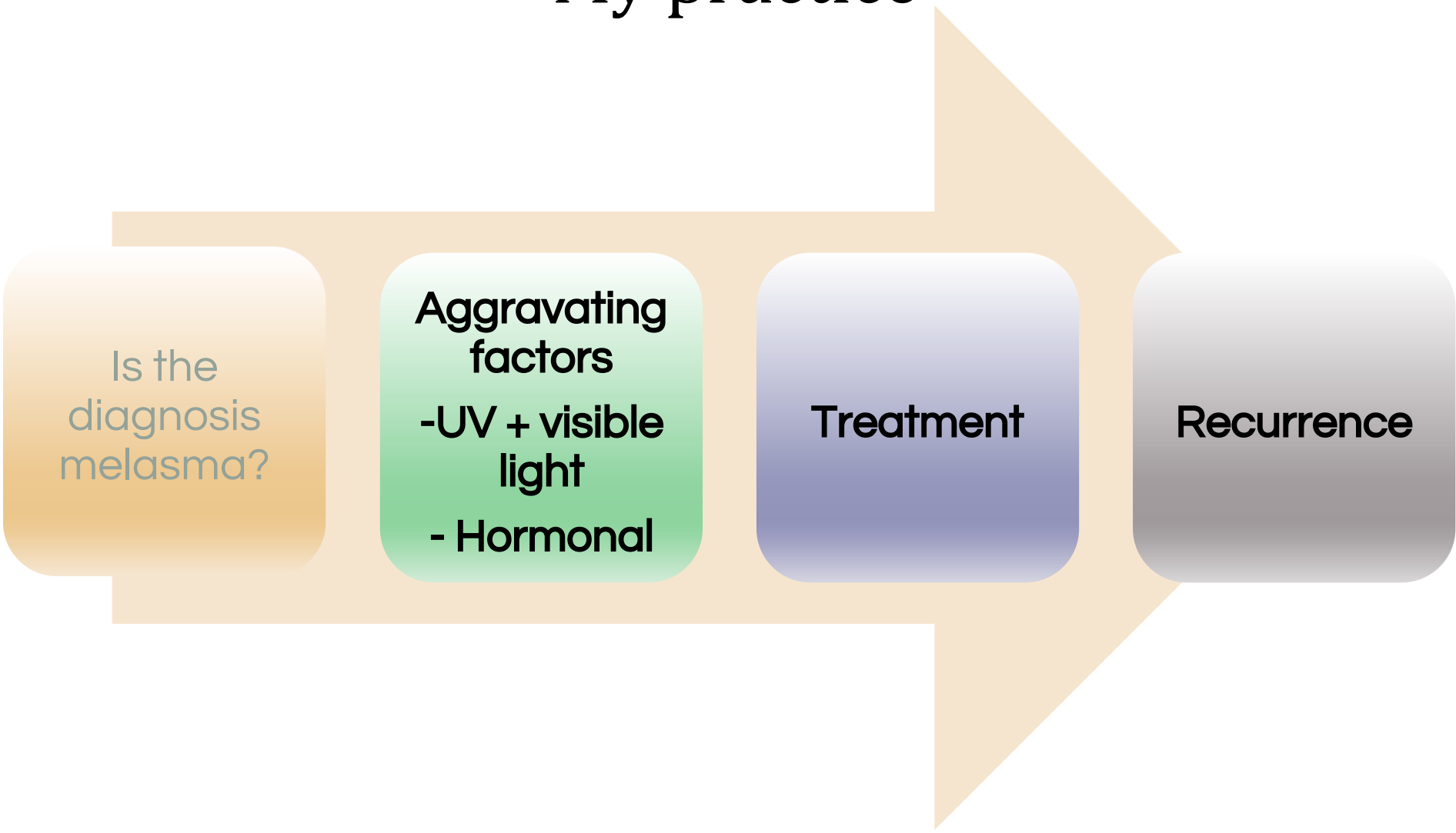
Overview

- ✓ Melasma – who what where why?
- ✓ Evidence for what treatments work- Cochrane systematic review
- ✓ New key trials
- ✓ My practice and pitfalls

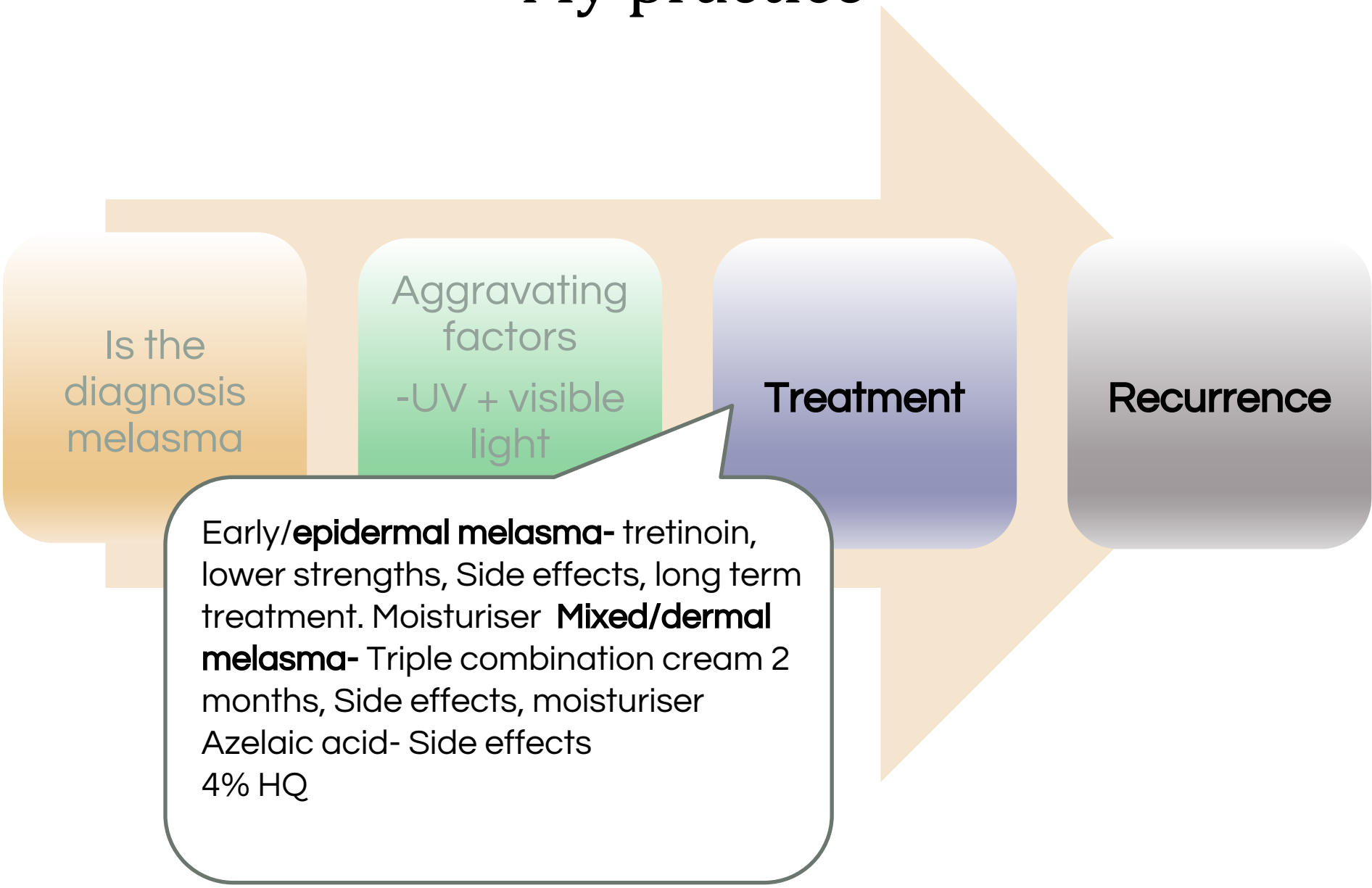
My practice


Is the diagnosis melasma?
Aggravating factors
-UV + visible light
- Hormonal
Treatment
Recurrence

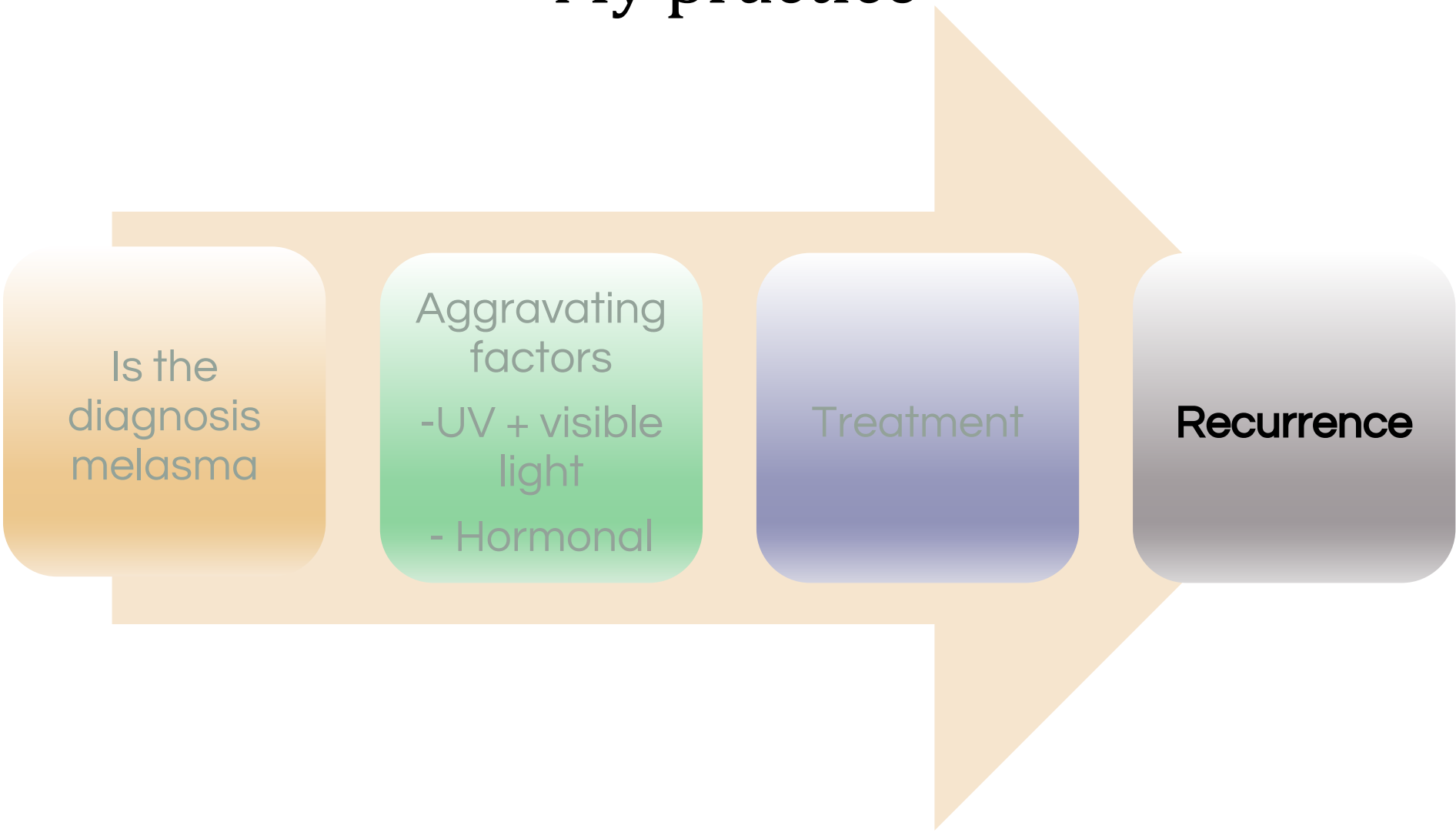
My practice


Is the diagnosis melasma?
Aggravating factors
-UV + visible light
- Hormonal
Treatment
Recurrence

My practice


Is the diagnosis melasma
Aggravating factors
-UV + visible light
Treatment
Recurrence
Early/**epidermal melasma-** tretinoin, lower strengths, Side effects, long term treatment. Moisturiser **Mixed/dermal melasma-** Triple combination cream 2 months, Side effects, moisturiser
Azelaic acid- Side effects
4% HQ

My practice


Is the diagnosis melasma
Aggravating factors
-UV + visible light
- Hormonal
Treatment
Recurrence

Thank you

Ratna_rajaratnam@cgh.com.sg