

HS ETİYOPATOJENEZİ

Prof. Dr. Murat Borlu
Erciyes Üniversitesi Dermatoloji





HS NEDİR X NE DEĞİLDİR ?

Hidros (ter)

Aden (bez)



Hidradenitis Suppurativa

Diğer kullanılan isimler

Akne İnversa

Vernueil Hastalığı

Ektopik Akne

Piyoderma Fistulans Signifika

Fox-Den Hastalığı

HS ne değildir?

- Apokrin bezlerden başlamaz!
- Primer enfeksiyon değil!
- Akne değildir!



HS & Enfeksiyon

- HS klasik 'enfeksiyon' değildir....
 - Tek bir patojen değil, polimorf flora vardır
 - Koagülaz Neg Staf. + Anaeroblar
 - Lenfadenopati görülmez
 - Baştaki steril sürece... enfeksiyon eklenmesi ile olur

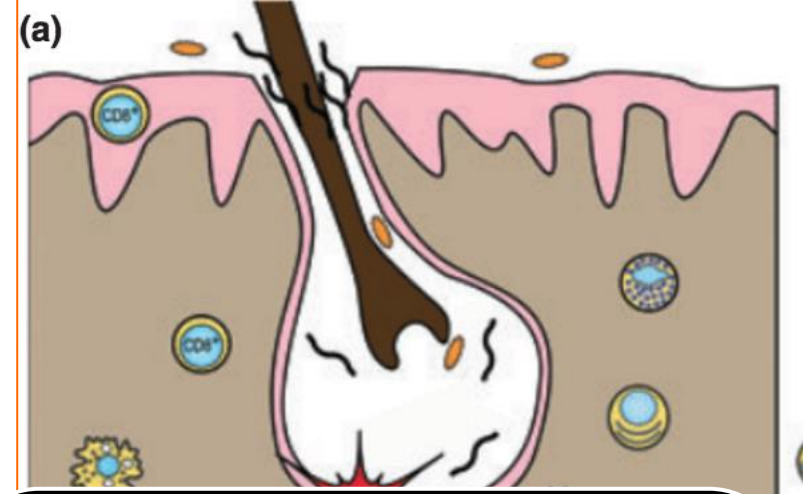
Foliküller Oklüzyon



Folikül Ruptürü



Şiddetli İnflamasyon



Komensal bakterilere karşı aberran keratinosit cevabı?



Yıllar İerisinde Gelişen HS Bilinirliđi



HS'nin Görüldüğü Bölgeler

Koltuk altı



Meme



Kasık

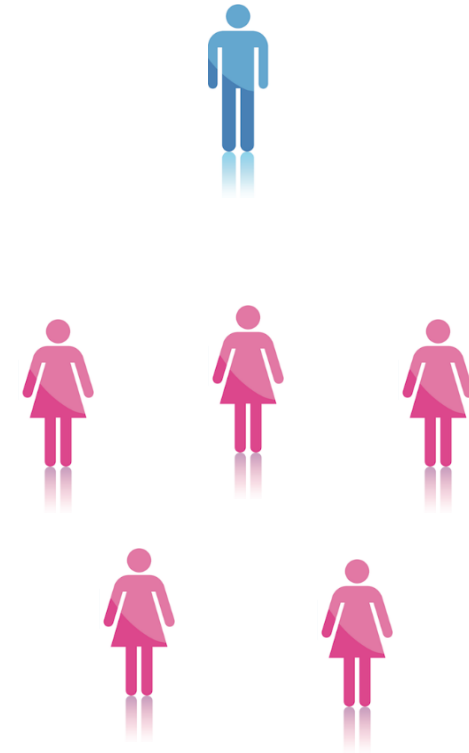
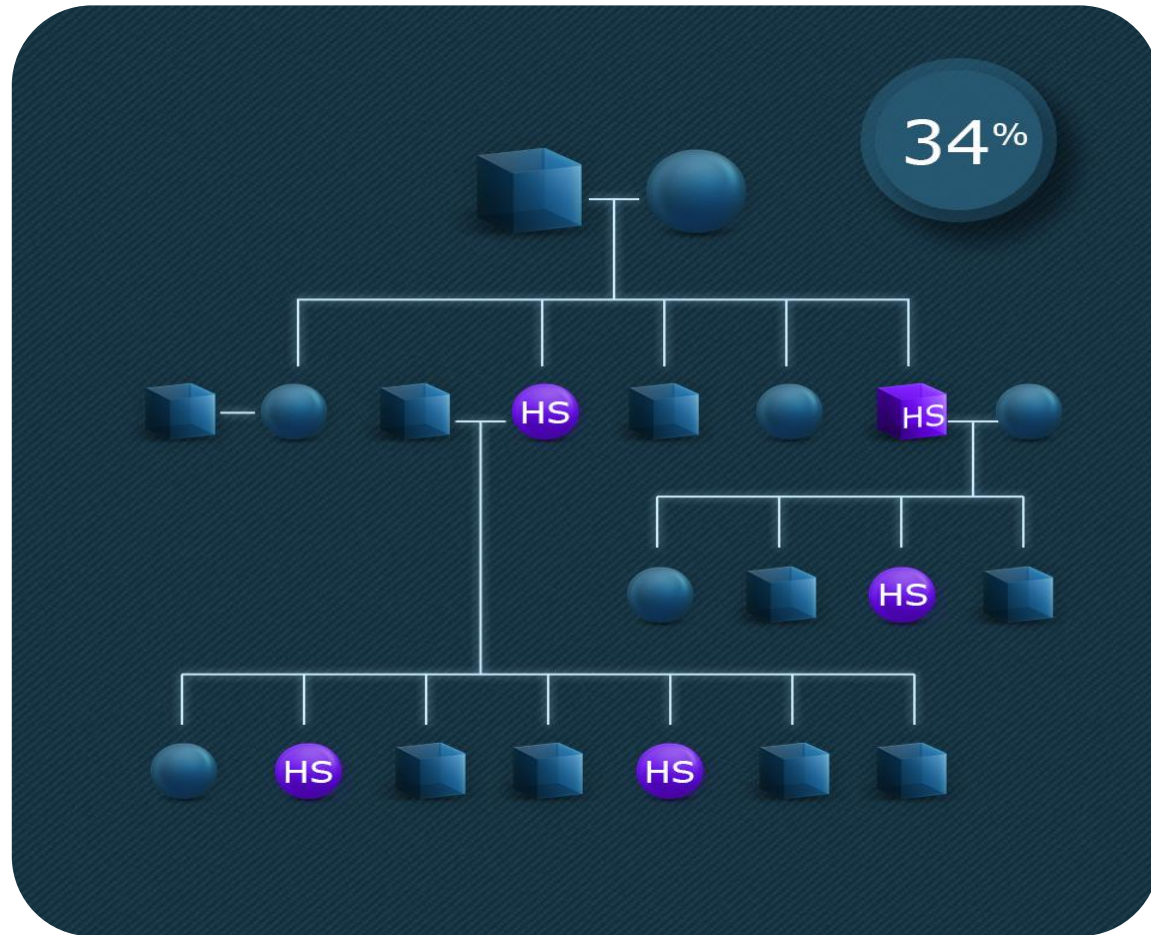


Perianal ve perineal bölge



Fransa	%1
Danimarka	%1
İsveç	% 0,15
ABD	%0,053
ABD	% 0,13

Genetik



HS: Anormal Sitokin Profili



	IL-1 β (pg/mL)	IL-10 (pg/mL)	TNF α (pg/mL)
HS	31	34	5
Psoriasis	4	2	1

IL-1 β -IL-23/ Th17/IL-17
yolakları önemli görünüyor

IL-1 β \uparrow
IL-23 \uparrow
IL-17 \uparrow

Risk Faktörleri – Biyolojik ve Çevresel Etkenler

Biyolojik Faktörler

Vücut Kitle İndeksi (Risk oranı* = 4.42)

Hormonlar

Genetik

Çevresel Faktörler

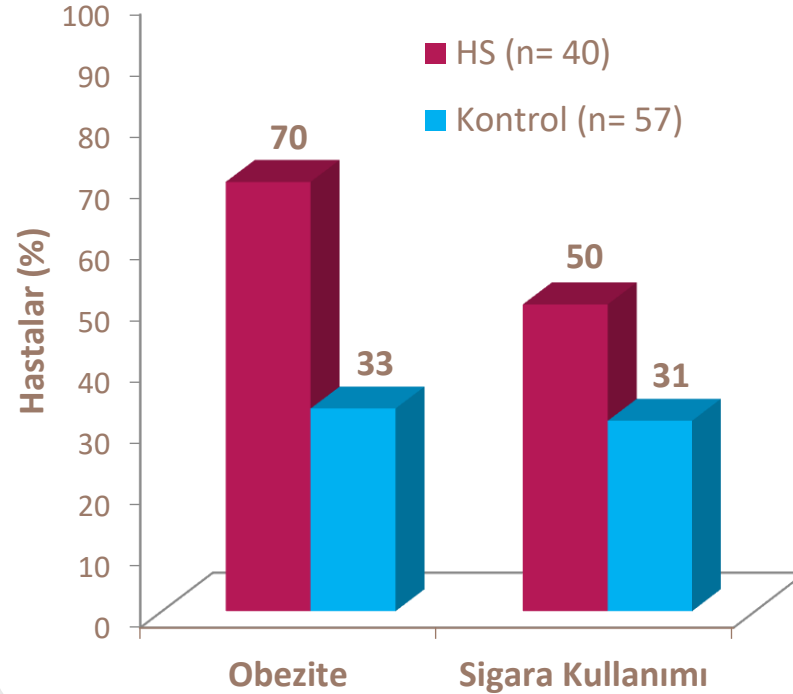
Sigara kullanımı (Risk oranı* = 12.55)

Lityum

Bakteriler

* vs. kontrol

Johns Hopkins Klinik Araştırması



Obezite

Sürtünme

Deri-deri
Deri- giysi

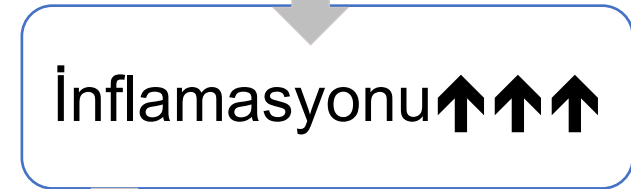
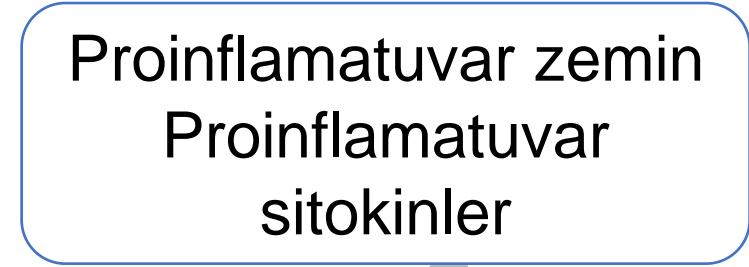
Mekanik sinyaller;
İlgili gen aktivasyonu

Lokal deri irritasyonu
Ter retansiyonu
İntrafolliküler akantoz
Keratinizasyon↑

Proinflamatuar zemin
Proinflamatuar
sitokinler

Proinflamatuar
sitokinler

İnflamasyonu↑↑↑

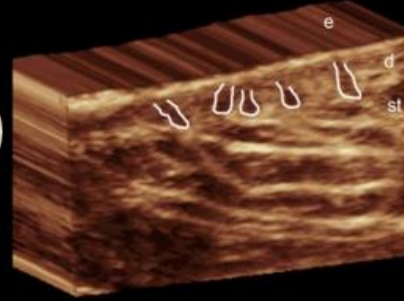


HS- Hastalık Şiddetini Belirleme

Hurley Evre 1:



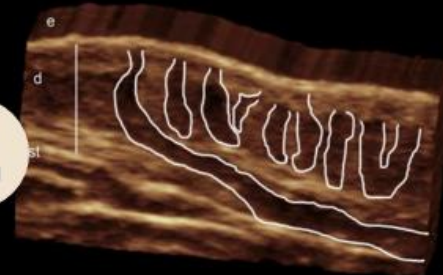
1



Hurley Evre 2:
lezyonlar birbi



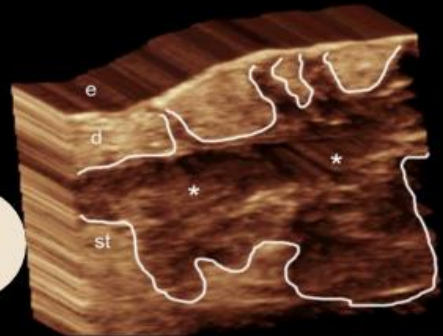
2



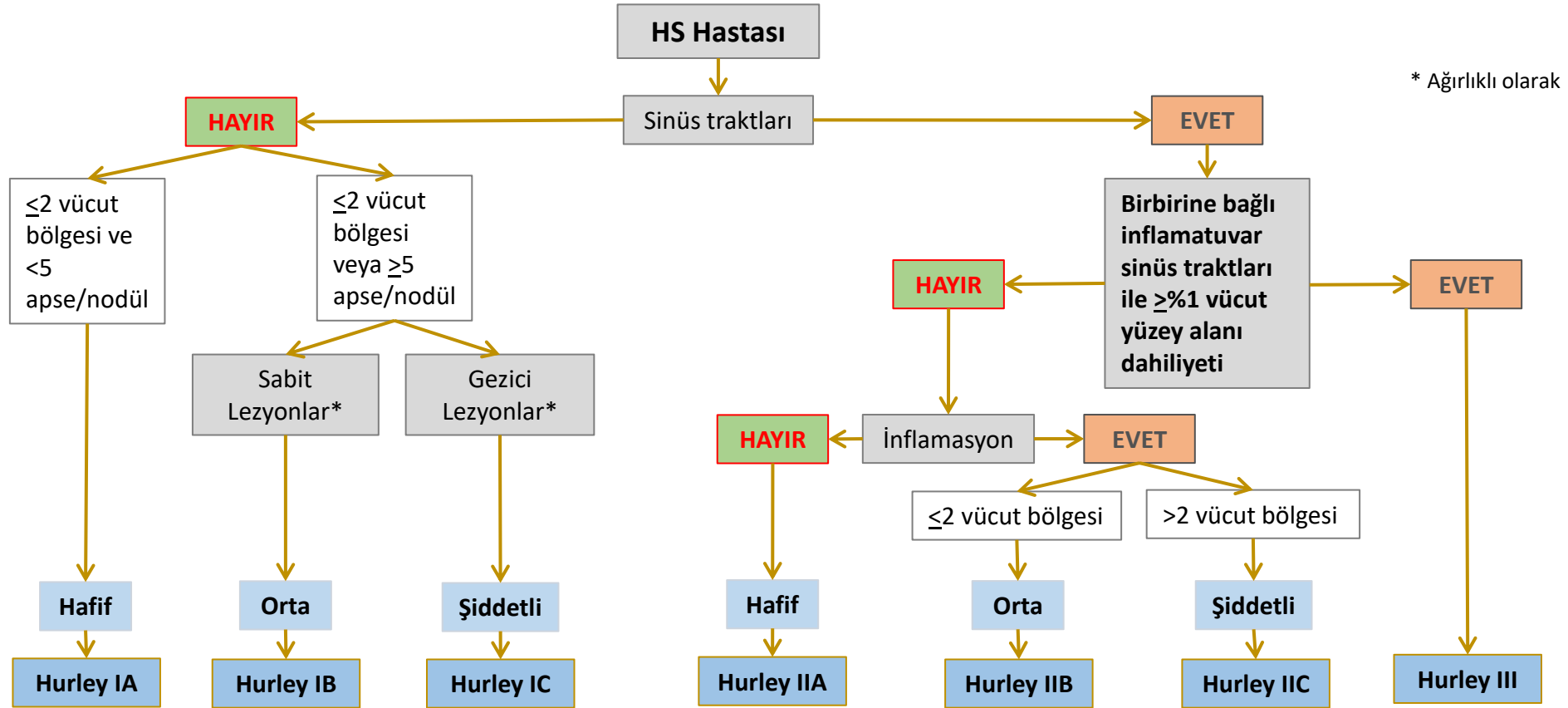
Hurley Evre 3:
traktlar, skarlar

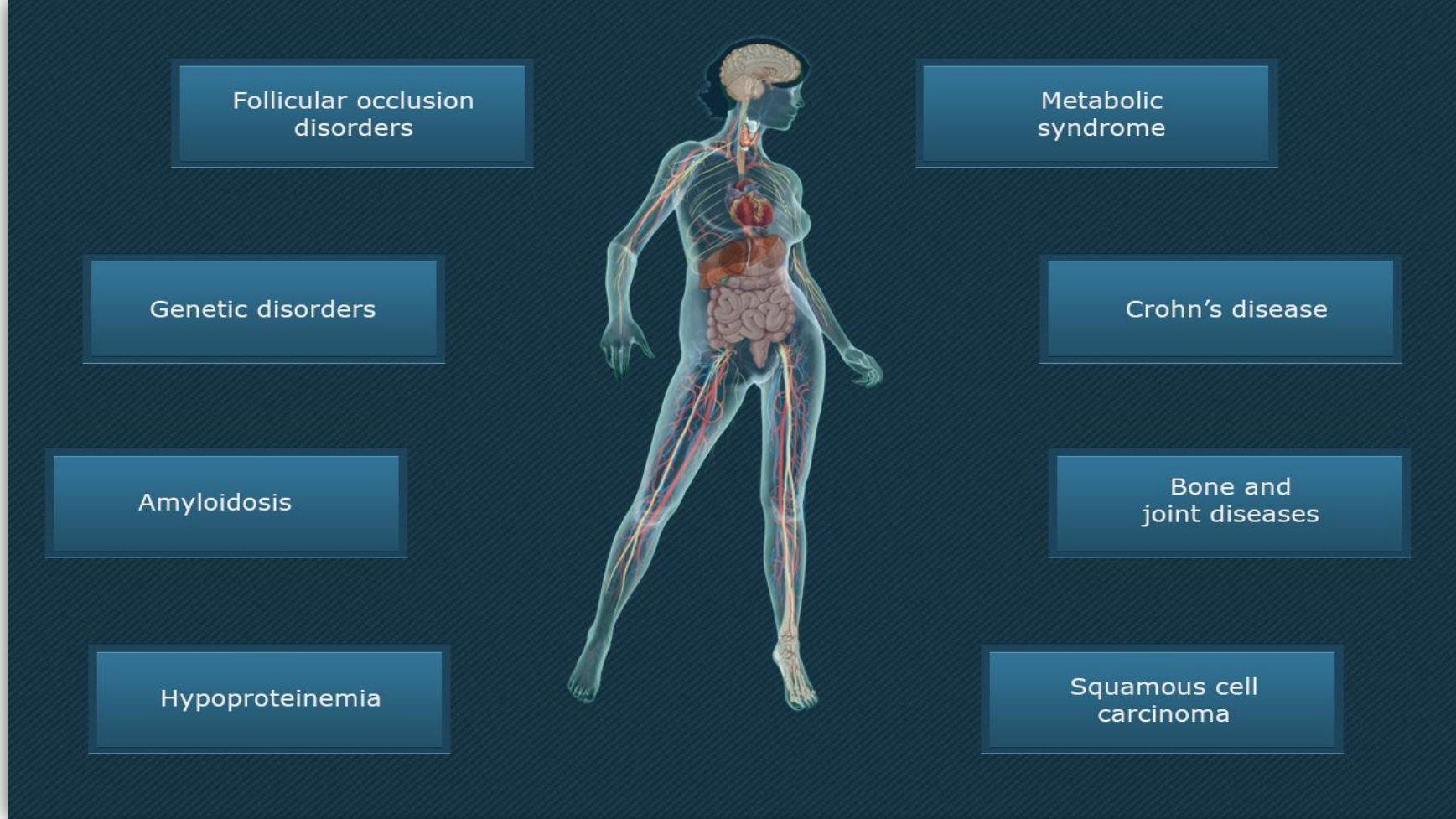


3



Geliştirilmiş Hurley Sınıflandırması





- Ortalama tanı alma süresi: 8 yıl
- Tanı için ortalama muayene sayısı 17
- Ortalama 3 farklı disiplin ve 5 farklı doktor

KOMPLİKASYON ve RİSKLER

> 3 x daha yüksek kalp krizi veya inme riski

- > 5 x daha yüksek tip 2 diyabet riski

> 2.5 x daha yüksek oranda ölüm vakası

- Lenfatik obstrüksiyon, lenfödem

Scc gelişimi 10-30 yılda... gluteal bölge

Romatolojik sıkıntılar.. Artrit..

HS TEDAVİSİ

Prof. Dr. Murat Borlu Erciyes Üniversitesi Dermatoloji



A Comparison of International Management Guidelines for Hidradenitis Suppurativa

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Published online: October 23, 2019

Aleksi J. Hendricks^a Jennifer L. Hsiao^b Michelle A. Lowes^c Vivian Y. Shi^d

European Academy of Dermatology and Venereology	2015	European S1 guideline for the treatment of hidradenitis suppurativa and acne inversa [25]	European S1
European HS Foundation	2016	Evidence-based approach to the treatment of hidradenitis suppurativa and acne inversa, based on the European guideline [24]	European HS Foundation
Swiss consensus group	2017	Swiss practice recommendations for hidradenitis suppurativa/acne inversa [26]	Swiss
Canadian Dermatology Association consensus group	2017	Approach to the management of hidradenitis suppurativa: a consensus document [23]	Canadian consensus
British Association of Dermatologists	2018	British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (2018) [18]	British
Canadian Dermatology Association	2018	Hygiene, debridement, and medical management: a level model of care and an integrative approach to hidradenitis suppurativa disease [22]	Canadian Dermatology Association
HS ALLIANCE		Hidradenitis suppurativa/acne inversa: a practical framework for clinical management optimization - systematic review and recommendations from the HS ALLIANCE working group [21]	HS ALLIANCE
US and Canadian Hidradenitis Foundations		North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian hidradenitis suppurativa foundations Part I: diagnosis, evaluation, and the use of complementary and procedural management [19] Part II: topical, intralesional, and systemic medical management [20]	North American
Brazilian Society of Dermatology	2019	Consensus on the treatment of hidradenitis suppurativa – Brazilian Society of Dermatology [27]	Brazilian

TNF-alpha
inhibitors

Lifestyle
advice

Immuno-
suppressive
therapy

Surgery

Antibiotics

Analgesia

Oral
retinoids

Antiandrogens
(Oral
contraceptives)

Psychological
support

- Yes
- No
- Maybe









Dr. Samuel Franco

BİLİMSEL OLAYLAR SCIENTIFIC EVENTS

DOI: 10.5336/dermato.2020-80699

Türkiye Hidradenitis Süpürativa Tanı ve Tedavi Kılavuzu

The Turkish Guideline for the Diagnosis and Management of Hydradenitis Suppurativa

 Murat BORLU^a,  Erkan ALPSOY^b,  Nilgün ATAKAN^c,  Emel Bülbül BAŞKAN^d,  Burhan ENGİN^e,
 Beyza ÖZÇINAR^f,  Fatma Figen ÖZGÜR^g,  Metin ÇAKMAKÇI^h

^aErciyes Üniversitesi Tıp Fakültesi, Deri ve Zührevi Hastalıkları ABD, Kayseri, TÜRKİYE

Hidradenitis suppurativa

Current and emerging treatments

J AM ACAD DERMATOL

Samantha R. Goldberg, BA,^a Bruce E. Strober, MD, PhD,^{b,c} and

Michael J. Payette, MD, MBA^{a,b,d}

Farmington, Cromwell, and New Haven, Connecticut



Adjuvan Tedaviler

- Genel tedbirler
- Bandajlar
- Psikososyal Destek
- **Kilo verme /sigara bırakma**

Medikal Tedaviler

- **Topikal Tedavi-Antibiyotik Dışı**
 - Exfoliyantlar ve Soyucular
 - Diğerleri
- **Topikal Antibiyotikler**
 - Klindamisin
- **Sistemik Antibiyotikler**
 - Tetrasiklin
 - Klindamisin, Rifampisin
 - Rifampisin, Moxifloxacin, Metronidazol
 - ertapenem

Anti-İnflamatuvar Tedaviler

- İntralezyonal Kortikosteroidler
- Sistemik Kortikosteroidler
- Siklosporin-A
- Hormonlar
- Analjezikler
- NSAİD
- Dapson
- Opiatlar
- Çinko
- Kolşisin
- Retinodiler
- İsoetretinoin
- Asitretin

Cerrahi Tedavi

- Konvansiyonel Cerrahi
- Deroofing
- Total eksizyon

Biyolojikler

- Adalimumab
- İnfliksimab
- sekukinumab
- Etanersept
- ustekinumab
- Anakinra
- IVIG

Lazerler

Karbondioksit Lazer

Nd-Yag Lazer

IPL

Fotodinamik Tedavi

Deneysel Tedaviler

- Botulinum Toksini

Gelecek Tedaviler

- IL-17 inhibitörleri
- IL-23 inhibitörleri
- Aprelimast

Topikal Tedaviler

Klindamisin, Klindamisin +rifampisin

- B önerme kanıt seviyesi II

Resorsinol % 15 evre 1-2

- Tüm hastalar ağrıda anlamlı düzelme yaşamıştır
- Ağrılı inflamatuvar nodüllerinin ortalama süresinde azalma

Adapalen, Azeleik asit, benzoil peroksit

- Uzman görüşü..... çalışma yok....

İLKS

Triamsinolon asetonid

2 haftada bir enjeksiyon, 48-72 saat etki eder.
Bakteriyel enfeksiyon varlığında kontendikasyon..

Tedavi amaçları:

Ağrı ve inflamasyonu azaltma; sıklıkla küratif değil
Püstülleri iğne inzisyon bölgesinden ekstra eder
Sinus ve traktların skarlı bölgeye kollaps yada transformu

Literatür:

Anekdotal

IV, D

Sistemik Antibiyotikler

- Tetrasiklin II B
- Klindamisin + Rifampisin II B
- Ertapenem (az bildirim ama etkili) IV C
- Metronidazole ?
- Minosiklin/Rifampisin C
- Kinolon / Rif/ Metronidazol IV C
- Dapson ??? IV C

Antiinflamatuvarlar

- Sistemik Kortikosteroidlertek başına etkisi ??
- Siklosporin-A
- Hidroksiklorokin
- Hormonlar
- NSAİD
- Çinko
- IVIG
- Kolşisin
- İsoetretinoin
- Asitretin
- Fumaratlar
- Antidiyabetikler, metformin..
- PDGF, GCSF

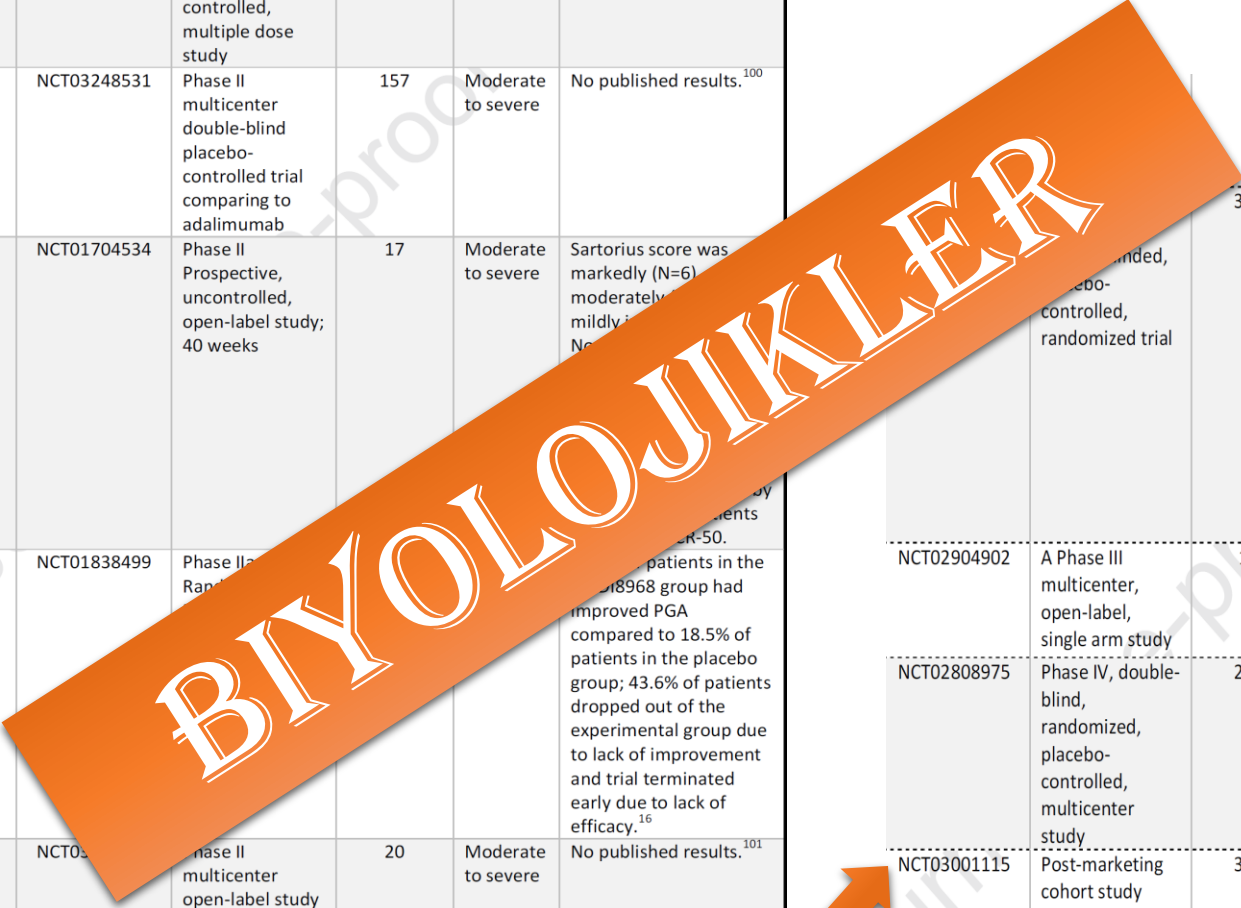
Antiandrojen

- Antiandrojenler, estrojen iyi geliyor
- Progesteron kötü geliyor
- Ethinyl estradiol/siproteron asetat kombinasyonu 29% iyileşme
- Polikistik over + prekoks puberte olan hst:
- Finasterid
- Dutasterid

Çinko Glukonat

- (90 mg/gün)
- 22 Hurley evre I ve II HS hastasının 8'inde tam, 14'ünde kısmi remisyon
- Doğal immün göstergenin ekspresyonunda anlamlı artış.. Etki: Potansiyel, düşük riskli ek tedavi; yaygın bir ek tedavi

Etanercept 50mg SQ	Fusion protein that binds and inhibits both TNF-α and TNF-β	NCT00107991	Phase II open-label; 12 weeks	15	Moderate to severe	Failed to show a clinically significant decrease in PGA score and DLQI at 12 weeks. ⁹⁸
CJM-112	Monoclonal antibody against IL-17A	NCT02421172	Phase II randomized, double-blind, placebo-controlled, multiple dose study	66	Moderate to severe	No published results. ⁹⁹
Bimekizumab	Monoclonal antibody against IL-17A and IL-17F	NCT03248531	Phase II multicenter double-blind placebo-controlled trial comparing to adalimumab	157	Moderate to severe	No published results. ¹⁰⁰
Ustekinumab 45mg or 90mg on weeks 0, 4, 16, 28	Monoclonal antibody against p40 subunit of IL-12 and IL-23	NCT01704534	Phase II Prospective, uncontrolled, open-label study; 40 weeks	17	Moderate to severe	Sartorius score was markedly (N=6), moderately, mildly improved. No published results. ¹⁰¹
MEDI8968	Antibody to the IL-1 receptor	NCT01838499	Phase IIa Randomized, double-blind, placebo-controlled, multicenter study	150	Moderate to severe	Patients in the MEDI8968 group had improved PGA compared to 18.5% of patients in the placebo group; 43.6% of patients dropped out of the experimental group due to lack of improvement and trial terminated early due to lack of efficacy. ¹⁶
Bermekimab 400 mg	Monoclonal antibody against IL-1α	NCT03001115	Phase II multicenter open-label study	20	Moderate to severe	No published results. ¹⁰¹
Adalimumab	Human monoclonal antibody against TNF-α	PIONEER I (NCT01468207)	Phase III multicenter, double-blinded, placebo-	307	Mild to severe	41.8% of patients receiving ADA compared to 26.0% of patients in the placebo group,



				326	Mild to severe	achieved a clinical response (P=0.003). ²⁹
						58.9% of patients receiving ADA compared to 27.6% of patients in the placebo group, achieved a clinical response (P=0.001). Patients receiving ADA had significantly greater improvement in lesions, pain, and modified Sartorius score compared to placebo group. ²⁹
NCT02904902	A Phase III multicenter, open-label, single arm study			15	Moderate to severe	No published results. ¹⁰²
NCT02808975	Phase IV, double-blind, randomized, placebo-controlled, multicenter study			200	Moderate to severe	No published results. ¹⁰³
NCT03001115	Post-marketing cohort study			300	severe	No published results. ¹⁰⁴

Secukinumab 300mg every 2 weeks or every 4 weeks	Monoclonal antibody against IL-17A	NCT03713632	Phase III, multicenter, randomized, double-blind, placebo- controlled, parallel group study	Estimated enrollment: 471	Moderate to severe	No published results. ³⁸
Guselkumab	Monoclonal antibody against IL-23	NCT03628924	A Phase II multicenter, randomized, placebo- controlled, double-blind, proof of concept study	Estimated enrollment: 180	Moderate to severe	No published results. ⁴²
Apremilast	PDE4 inhibitor that blocks cAMP degradation, which drives activation of PKA. In turn, it reduces production of TNF- α , IL- 12p40, and IL- 17, and increases IL- 10.	NCT03049267	Phase I double- blind, randomized placebo- controlled clinical trial	20	Moderate	No published results. ¹⁰⁶
		NCT02695212	Phase II single center open- label clinical trial	20	Moderate	No published results. ¹⁰⁷
		N/A No clinical trial underway	Case series	9	Moderate to severe	Significant improvement in Sartorius score in addition to decreased VAS pain score and DLQI. ¹⁰⁸
IFX-1	Monoclonal antibody against C5a	NCT03001622	Phase II open- label clinical trial	12	Moderate to severe	No published results. ¹⁰⁹

INCB054707	JAK Inhibitor	NCT03569371	Phase II open- label, single arm study	10	Infliximab 5mgs/kg at weeks 0, 2, 6, then every 8 weeks thereafter	Chimeric monoclonal antibody against TNF- α	NCT00795574	Phase II, randomized, double-blind, placebo- controlled crossover trial	38	Moderate to severe	60% of patients treated with IFX showed a 25% to less than 50% improvement, 26.7% showed a 50% or greater improvement, and 13.3% showed a less than 25% improvement in HSSI score 8 weeks after the initial dose. ¹⁰⁵
					Anakinra 100mg/0.67mL injected subcutaneously once daily	Humanized monoclonal antibody against the IL- 1 receptor	NCT01516749	Phase II, open- label, proof-of- concept, non- randomized Study	6	Moderate to severe	Patients showed a significant reduction of Sartorius Score after anakinra was given daily for 8 weeks ($p= 0.024$). ⁴⁴
							NCT01558375	Phase II, double- blind, randomized, controlled	20	Moderate to severe	HiSCR was improved at week 12 in 78% of patients in the anakinra arm compared to 30% in

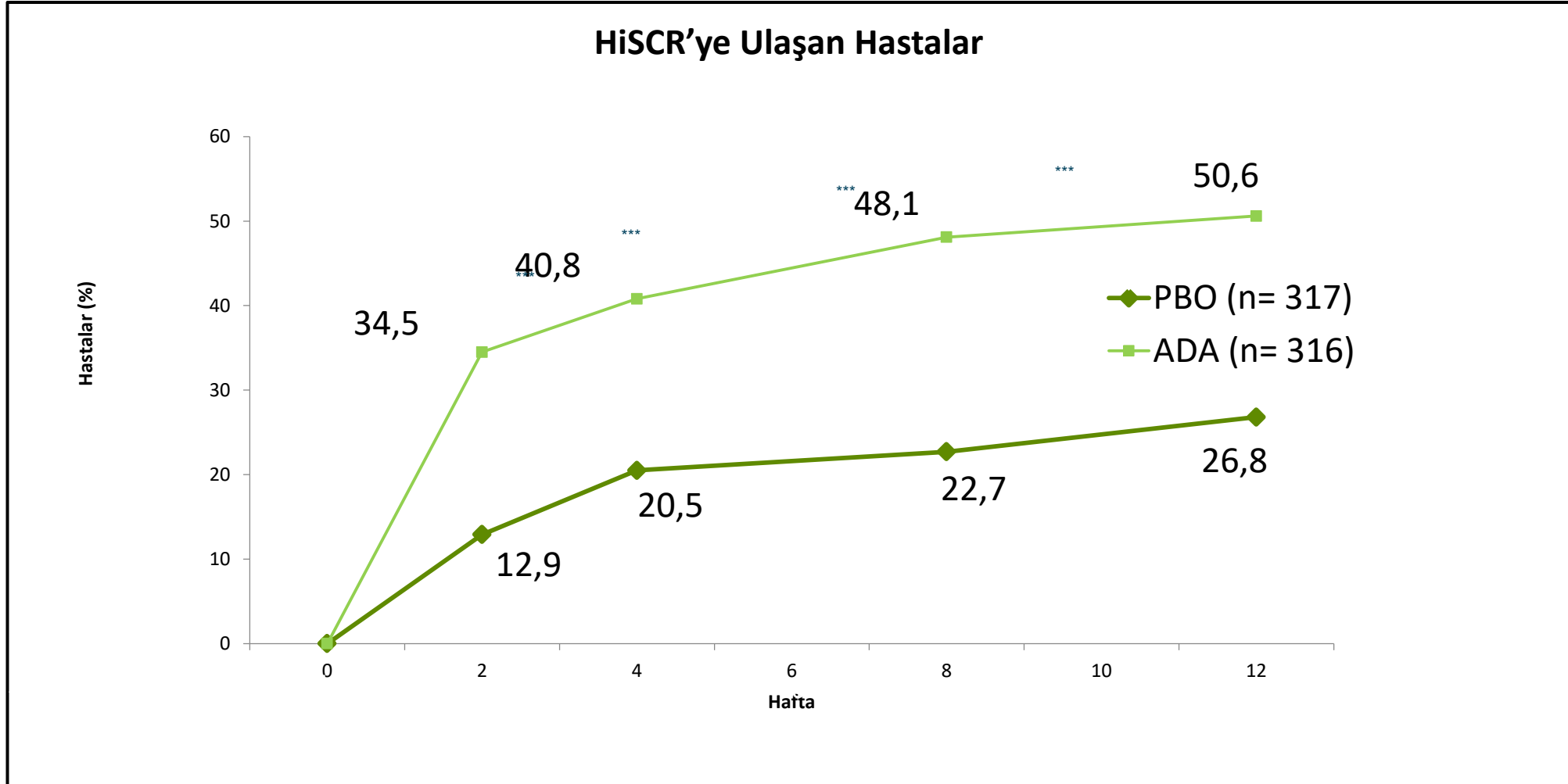
Biyolojikler

- Adalimumab
- İnfliksimab
- Etanersept
- Ustekinumab
- Anakinra
- Sekukinumab
- Guselkumab
- bimekizumab
- IVIG

Adalimumab

- 0.hft - 160 mg
- 2 hft - 80 mg
- 4. hft itibaren haftalık - 40 mg
- 16 hft içinde cevap alamazsan deęiřtir..
- Adalimumab, başarılı faz III çalışmalarının sonucunda orta ve ileri şiddet HS hastalarında onaylı ilk tedavi rejimidir.¹

PIONEER I ve II: Etkililik



Infliximab

- infliximab 5 mg/kg 0-2-6-8
- Cevap %80-89;
 - 8 hft iyileşme başlıyor; 13-45 hft \geq 50% iyilik
 - Relaps % 25; 37 hft sonra görülebiliyor
 - çalışma dizaynları onay için yeterli değil..
 - faz 3 çalışma

Adalimumab and infliximab survival in patients with hidradenitis suppurativa: a daily practice cohort study*

L.M. Prens¹, K. Bouwman,¹ P. Aarts,² S. Arends,³ K.R. van Straalen,² K. Dudink,² B. Horváth¹ and E.P. Prens²

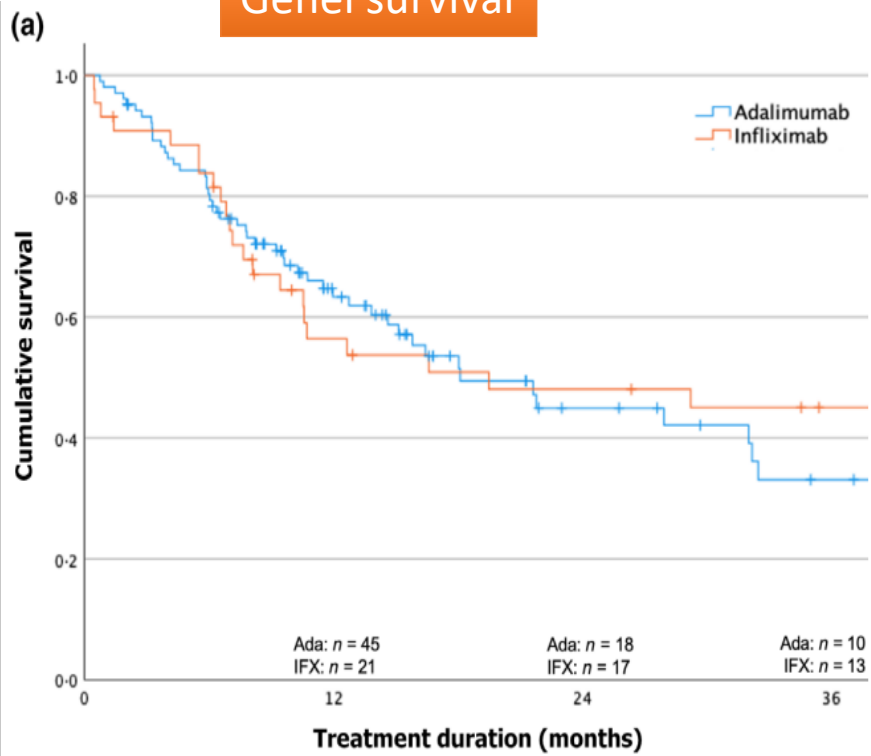
¹Department of Dermatology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

²Erasmus MC, University Medical Center Rotterdam, Department of Dermatology, Rotterdam, the Netherlands

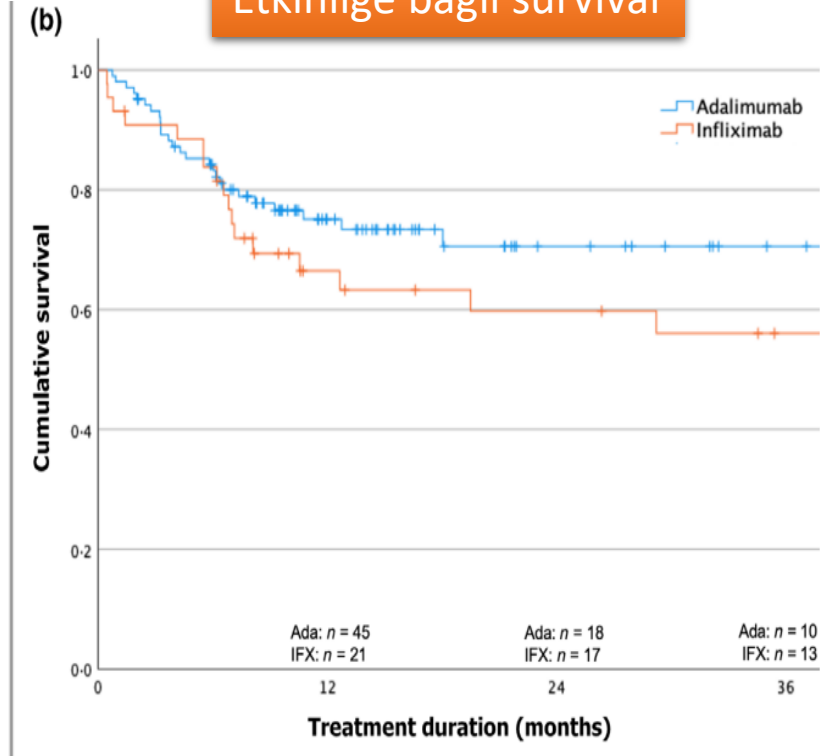
³Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, the Netherlands

Linked Comment: R. Hambly and B. Kirby. *Br J Dermatol* 2021; **185**:16–17.

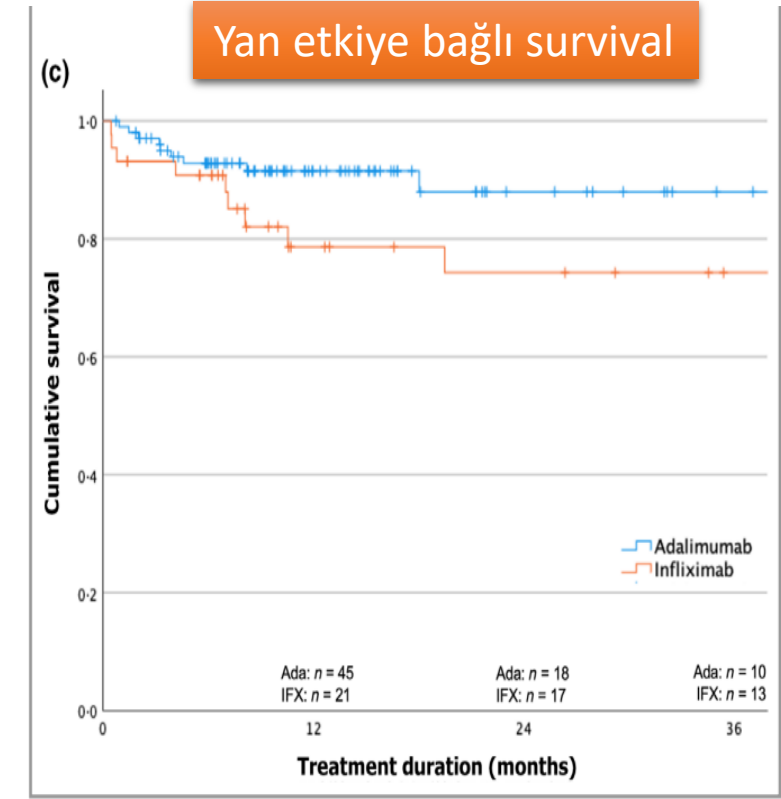
Genel survival



Etkinliğe bağlı survival



Yan etkiye bağlı survival

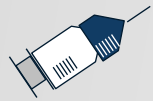


The SUNSHINE and SUNRISE Phase 3 Clinical Study Program

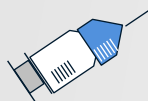
The largest Phase 3 trials conducted in HS to date

Phase 3

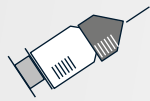
Two **randomized, double-blind, multicentre** studies assessing **short (16 weeks)** and **long-term (up to 1 year)** efficacy, safety, and **tolerability** of two s.c. **SEC** dose regimens in adult patients with **moderate to severe HS**



SEC 300 mg
Q2W



SEC 300 mg
Q4W



PBO

Study design

1,084* patients across **219[†]** sites **worldwide**



SUNSHINE (M2301), N=541 **SUNRISE (M2302), N=543**

Start



Jan 2019

LPLV



Jul 2022

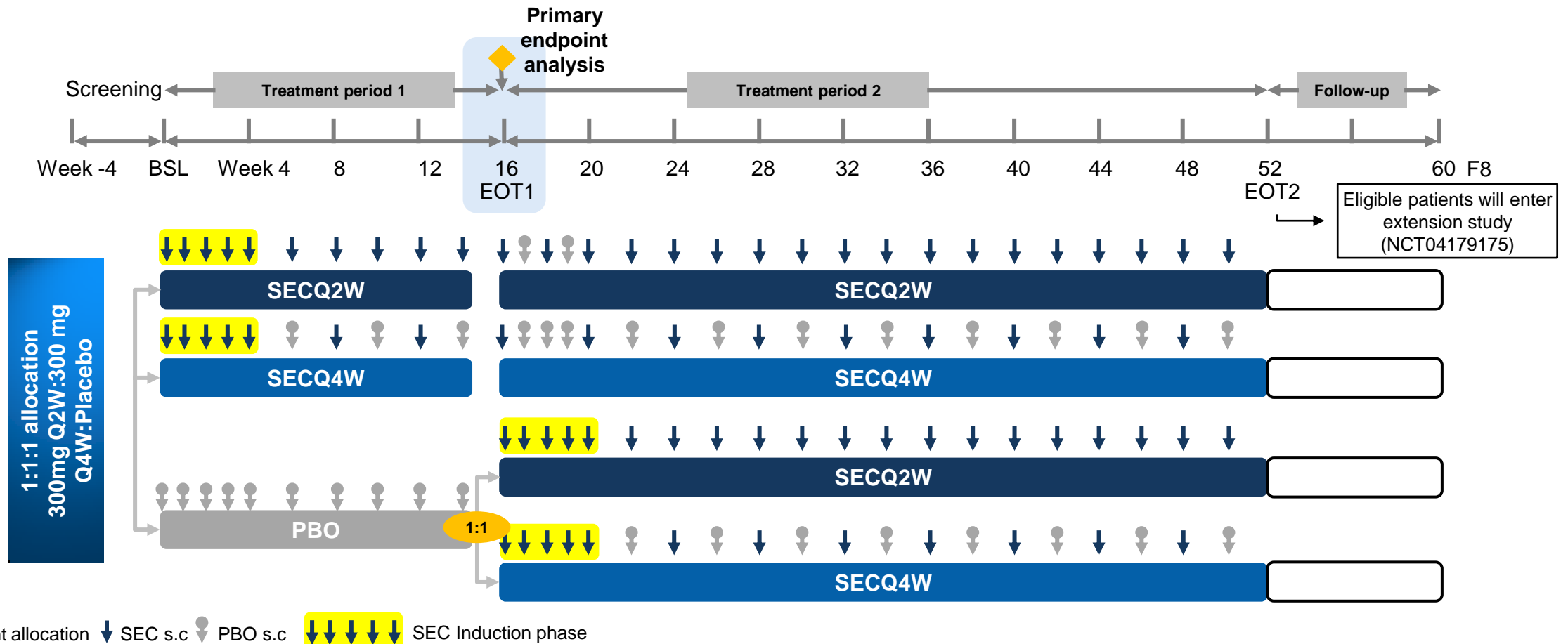
*patients randomized overall; †number of sites overall.

HS, hidradenitis suppurativa; LPLV, last patient last visit; N, number of patients; PBO, placebo; Q2W, every two weeks; Q4W, every four weeks; s.c, subcutaneous; SEC, secukinumab.

SUNSHINE and SUNRISE study design

Two identical Phase 3 trials

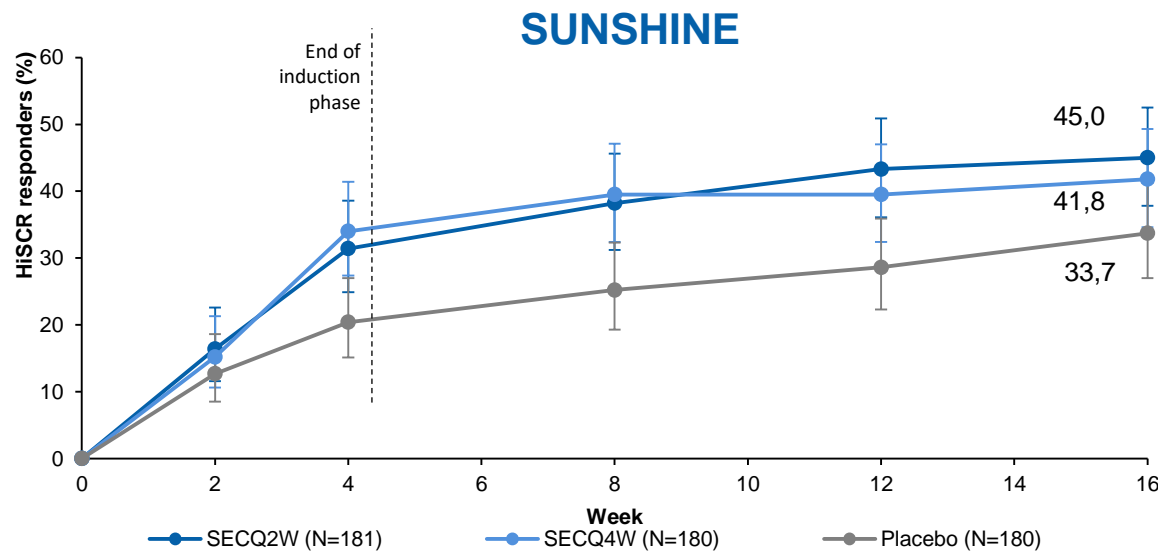
- Here, we present the **primary efficacy analysis (Week 16)** for SUNSHINE and SUNRISE



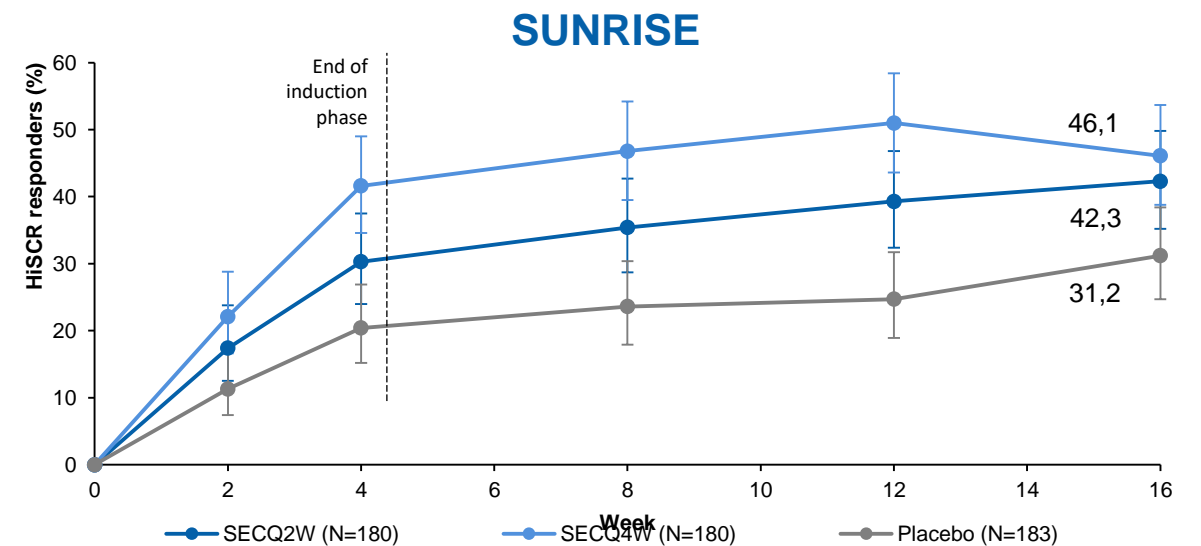
AN, abscess and inflammatory nodule; BSL, baseline; EOT1/EOT2: end of treatment period 1/2; F8, end of 8-week follow-up period; PBO, placebo; PRO, patient-reported outcome; Q2W, every two weeks; Q4W, every four weeks; s.c., subcutaneous; SEC, secukinumab 300 mg.

SUNSHINE and SUNRISE both met their primary endpoint (HiSCR)

- In both studies, **greater response rates for secukinumab** compared to placebo were seen **at all time-points** from Week 2 to Week 16, with a rapid onset of action by Week 2
 - Clinical response (HiSCR) to secukinumab is in line with sustained and continued improvement up to 52 weeks of treatment*



SECQ2W Wk 16	SECQ4W Wk 16	Placebo Wk 16
45.0% (p=0.0070)	41.8% (p=0.0418)	33.7%



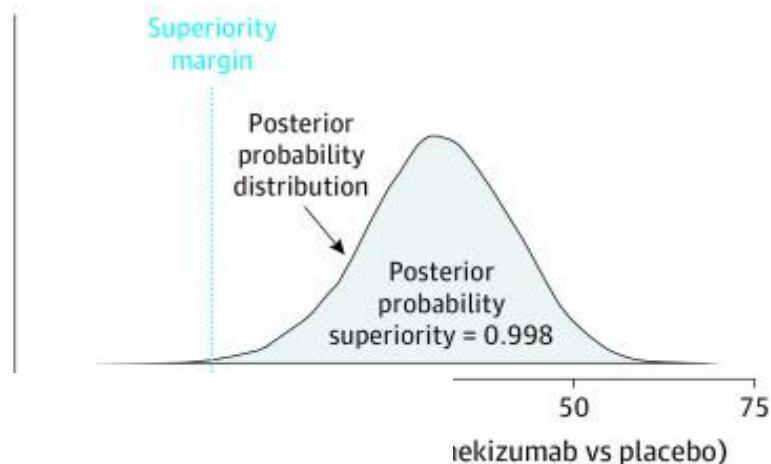
SECQ2W Wk 16	SECQ4W Wk 16	Placebo Wk 16
42.3% (p=0.0149)	46.1% (p=0.0022)	31.2%

*Long term data are based on an interim analysis where 95% of patients completed or discontinued by Week 52. One-sided nominal p-values are based on a logistic regression model, the primary estimand, and multiple imputation. Error bars represent 95% CIs. Green represents statistical significance and red represents non-significance compared with placebo. CI, confidence intervals; HiSCR, hidradenitis suppurativa clinical response; N, number of patients in group; Q2W, every two weeks; Q4W, every four weeks; SEC, secukinumab 300 mg; Wk, week.

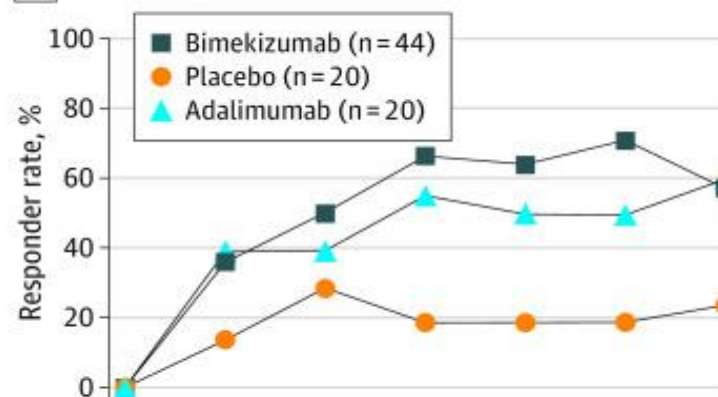
Efficacy and Safety of Bimekizumab in Moderate to Severe Hidradenitis Suppurativa

A Phase 2, Double-blind, Placebo-Controlled Randomized Clinical Trial

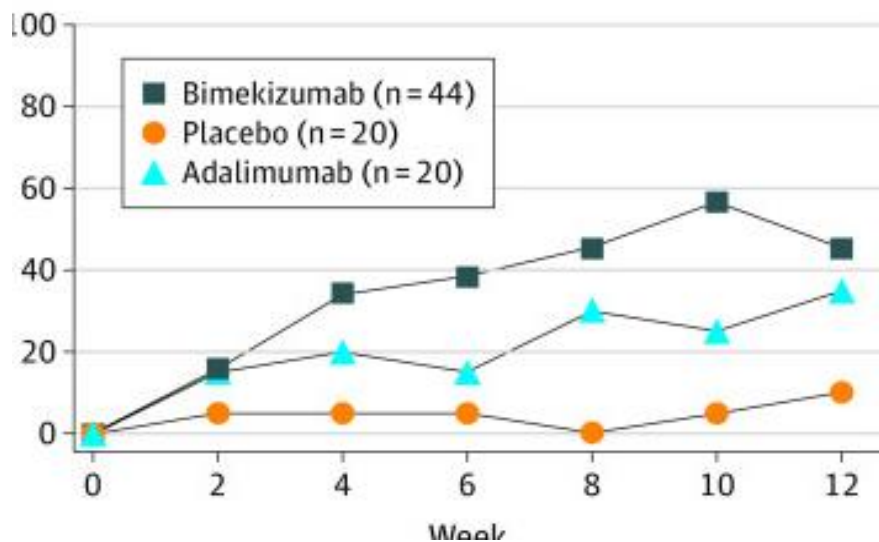
A Modeled posterior probability of superiority



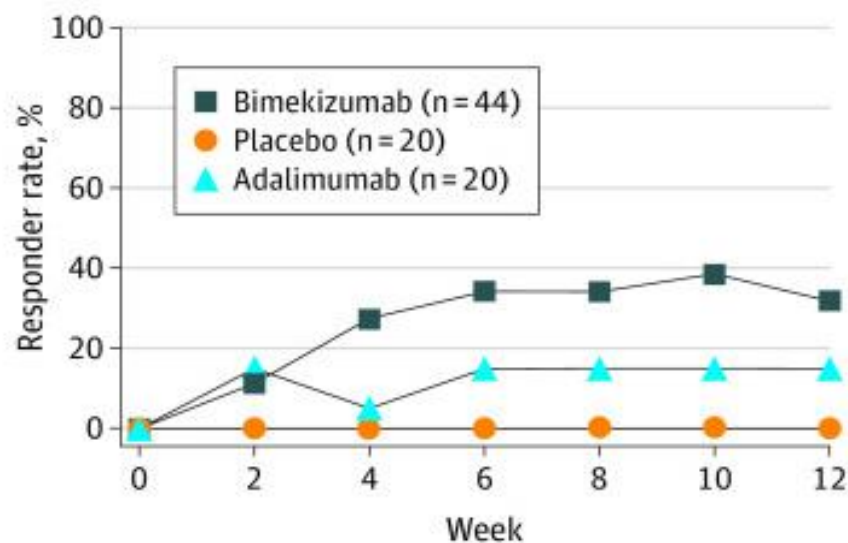
B HiSCR responders, NRI



HiSCR₇₅ responders, NRI



D HiSCR₉₀ responders, NRI



Biyolojikler

- **Ustekinumab:** Ustekinumab (0-4-16.haftalarda 45 mg sc enj. 1/3 hastada düzelme..
- **Etanercept :** etkisiz
- **Anakinra:** 8 haftada belirgin gerileme, 12. haftada HiSCR % 70
- **Bermekimab (anti IL-1 alfa):** devam ediyor
- **Guselkumab:** devam ediyor...
- **Apremilast :** devam ediyor
- **IFX-1 (anti c5a):** devam ediyor
- **JAK inh:** devam ediyor
- **IVIG:** sınırlı etki anektodal

HS & Lazerler

- Lazerle hastalıklı dokunun uzaklaştırılması

- CO2 Lazer Eksizyon
- CO2 Lazer Vaporizasyon

Ib, A

- ✓ Epilasyon sağlayarak tedavi desteği

- ✓ Nd:YAG Lazer
- ✓ Long-pulsed 755-nm Alexandrite Lazer
- ✓ Diode Lazer (1450 nm)
- ✓ Intense Pulsed Light

Ib, A

IV, D

Botulinium toksini

İzole HS vakalarında etkili

- Etki mekanizması bilinmiyor...
- Ter önleyici etkisinin veya pilosebaceöz unsurların fonksiyonunun azalması....
- Lezyonlara direkt enjeksiyon...
- Bazı vaka raporlarında başarılı, ancak büyük çalışmalar yok...

Cerrahi Tedaviler

- Deroofing IV D
- İnsizyon drenaj III C
- Ekzizyon primer onarım III C
- Eksizyon sekonder iyileşme II B
- Geniş eksizyon II B
- Rekons Flep I-II A,B
- STEEP IV D

Ađrı Yönetimi

HS ađrı kaynakları deđişebilir:

- İnflamasyon – apseler, kronik sinuslar, granülomlar
- Friksiyon
- Skarlaşma ve hiperkeratözden dolayı gerilme ađrısı
- Lenfödem
- Artrit

- NSAİD
- Opiatlar

**Medical therapy is the optimal treatment
for hidradenitis suppurativa**

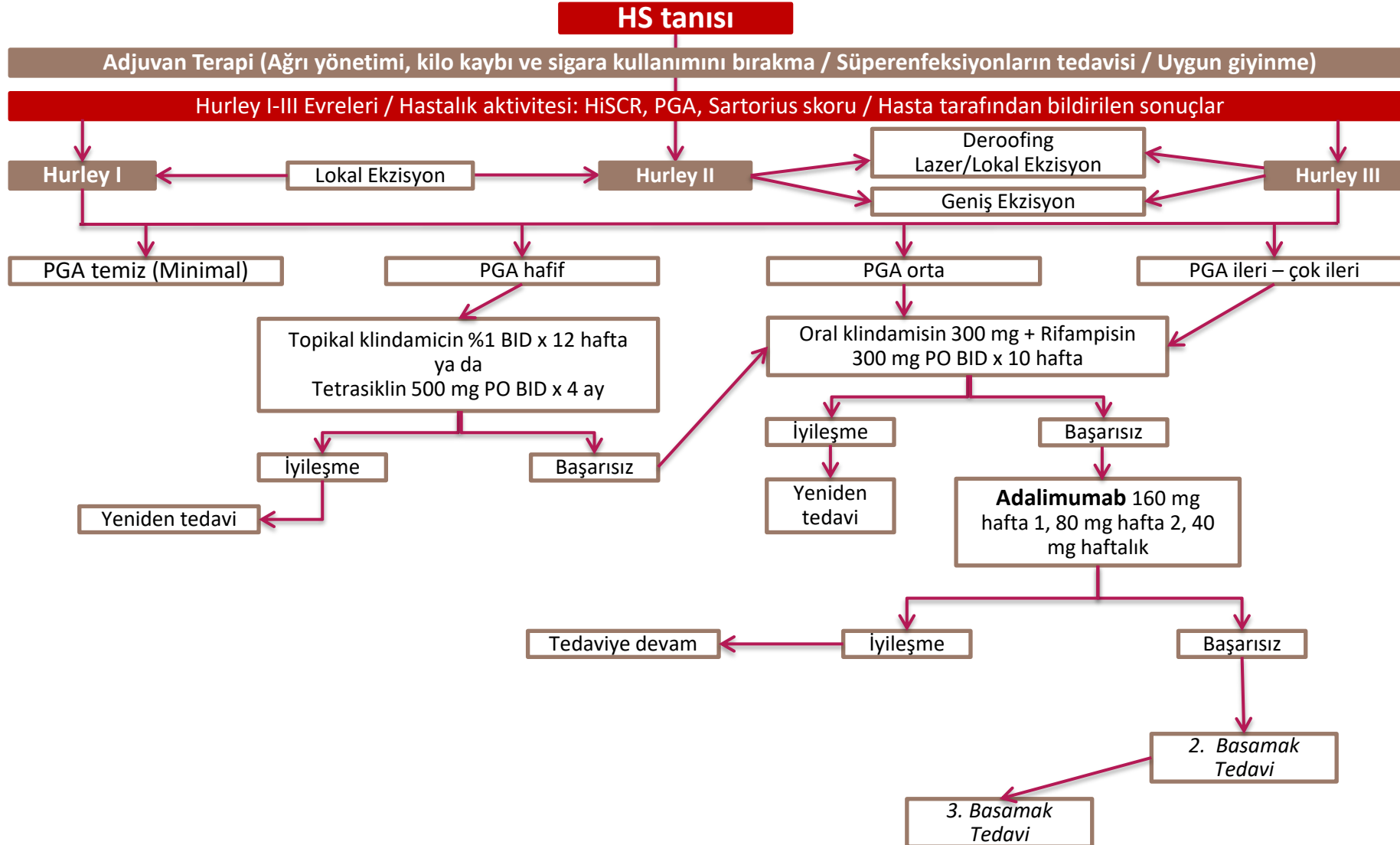


Steven Daveluy, MD
Detroit, Michigan

This article is part of a point-counterpoint series of controversies.

This scenario is similar to psoriasis, where it is only recently that the development of a wide treatment landscape with numerous very effective options has allowed us to make our treatment goal 1% of body surface area involvement or less. I am confident that, in time, **medical therapy will provide us with the ability to control HS without surgical intervention**

Kanıtı Dayalı HS Tedavi Algoritması - 2016



1. basamak



- Topikal klindamisin
- Oral klindamisin/rifampisin
- Oral tetrasiklin
- Adalimumab
- Cerrahi
- I

2. basamak



Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa

Wayne Gulliver^{1,2} · Christos C. Zouboulis^{1,3} · Errol Prens^{1,4} · Gregor B. E. Jemec^{1,5} · Thrasivoulos Tzellos^{1,6}

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3. basamak

- Klindamisin
- Antiandrojenler
- Kolşisin
- Btx



TEDAVI ?

Doctors Predicted

But Contrary
To Their Prediction

I Would Never Cure
My Hidradenitis Suppurativa

TEDAVI ?

I Cured HS Permanently
In Just 2 Months!



Orta- Şiddetli HS Olgularında



Topikal Klindamisin %1, 2x1, 3 ay
Tetrasiklin 500mgx2, 4 ay

Lazerler ?

Oral Klindamisin 300mg, 2x1
Rifampisin 600mg/gün
Ertapenem ?

Asitretin 25 mg/gün

Adalimumab; 160mg-0hft
80mg-2 hft

Infliksımab 5mg/kg

Sekukinumab 300 mg 2-4 hf

?

İkzekizumab, bimekizumab, guselkumab, Jak-İ, anti IL-1, 36

Şiddet

RESİPTİLER