DİRENÇLİ AAM TEDAVİSİNDE BOTULİNUM TOKSİNİ

Dr. Abdullah Demirtaş
Erciyes Üniversitesi Tıp Fakültesi
Üroloji Anabilim Dalı
Kayseri

Aşırı Aktif Mesane

- Tanım: idrar yolu enfeksiyonu veya başka herhangi bir patoloji olmaksızın, birlikte idrar kaçırmanın olduğu yada olmadığı acilen idrara sıkışma hissidir. Sık idrara çıkma ve noktüri eşlik eder.

Incontinence, 5th consult 2013

- Ürolojik kullanımında
  - 2011 yılında spinal kord hasarına veya multipl skleroz gibi nörojenik hastalıklarda FDA onayı almıştır
  - Ocak 2013 de aşırı aktif mesanede FDA onayı almıştır

30 Ağustos 2014 CUMARTESİ Resmî Gazete Sayı : 29104

TEBLİĞ

Sosyal Güvenlik Kurumundan:

SOSYAL GÜVENLİK KURUMU SAĞLIK UYGULAMA TEBLİĞİNDE DEĞİŞİKLİK YAPILMASINA DAİR TEBLİĞ

d) Sıkışma tipi üriner inkontinans, sıkışma ve sık idrar semptomları olan aşırı aktif mesane endikasyonunda, en az 2 farklı antikolinerjik/antimuskarinik tedaviyi 3 ay süre ile kullanıp tedaviye yanıt vermeyen ya da bu tedavileri tolereedemeyen hastalarda, bu durumu belirten ve kullanılacak ilacın dozuyla, kullanım süresini içeren üniversite hastaneleri ile eğitim ve araştırma hastanelerinde en az bir üroloji uzman hekiminin yer aldığı 3 ay süreli sağlık kurulu raporuna dayanılarak kullanılır. 3 ay süreli raporlar bir uygulama için olup, reçeteler üroloji veya kadın hastalıkları ve doğum uzman hekimleri tarafından

- Faz II, çok merkezli, çift kör, randomize, doz ayarlama çalışması, 313 hasta
- İdiopatik overaktif mesane,
- 50,100,150,200,300 U, intradetrusor onabotilinumtoxinA, plasebo
- 12 hafatada değerlendirme
- 100U doz güvenlik profili ve PVR için uygun bulunmuş

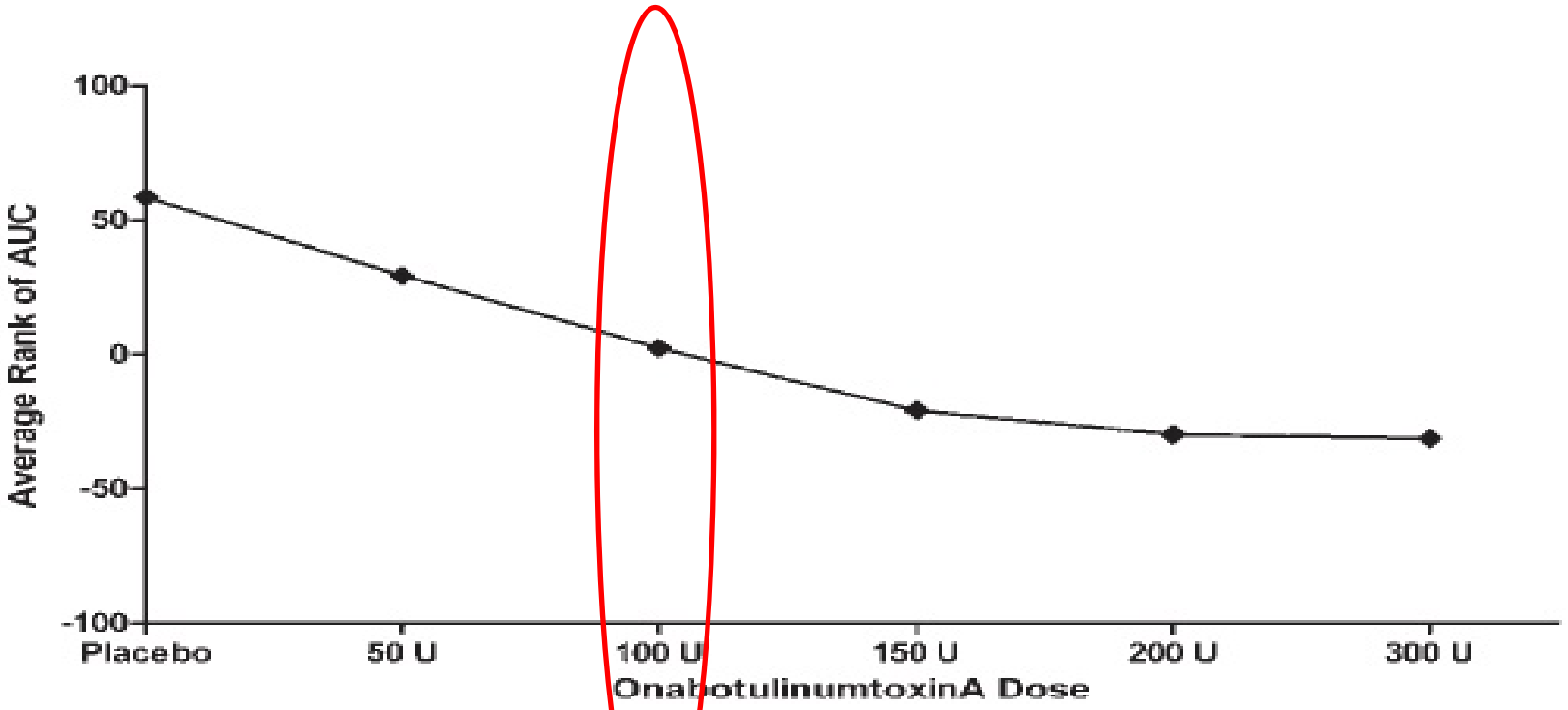


Figure 2. Dose response. Cumulative efficacy (AUC) using rank residual score of UUI episodes for all points.

Dmochowski 2010

Doz etkinlik

- Haftalık
  - İşeme sıklığında azalma
  - Noktüride azalma
  - İşenen volümde artış
- Etki 100 U ve üzerinde kalıcı
- Yaşam kalitesi memnuniyetinde başlangıç değerine göre anlamlı düzelme 100 U

Dmochowski 2010

Yaşam kalitesi

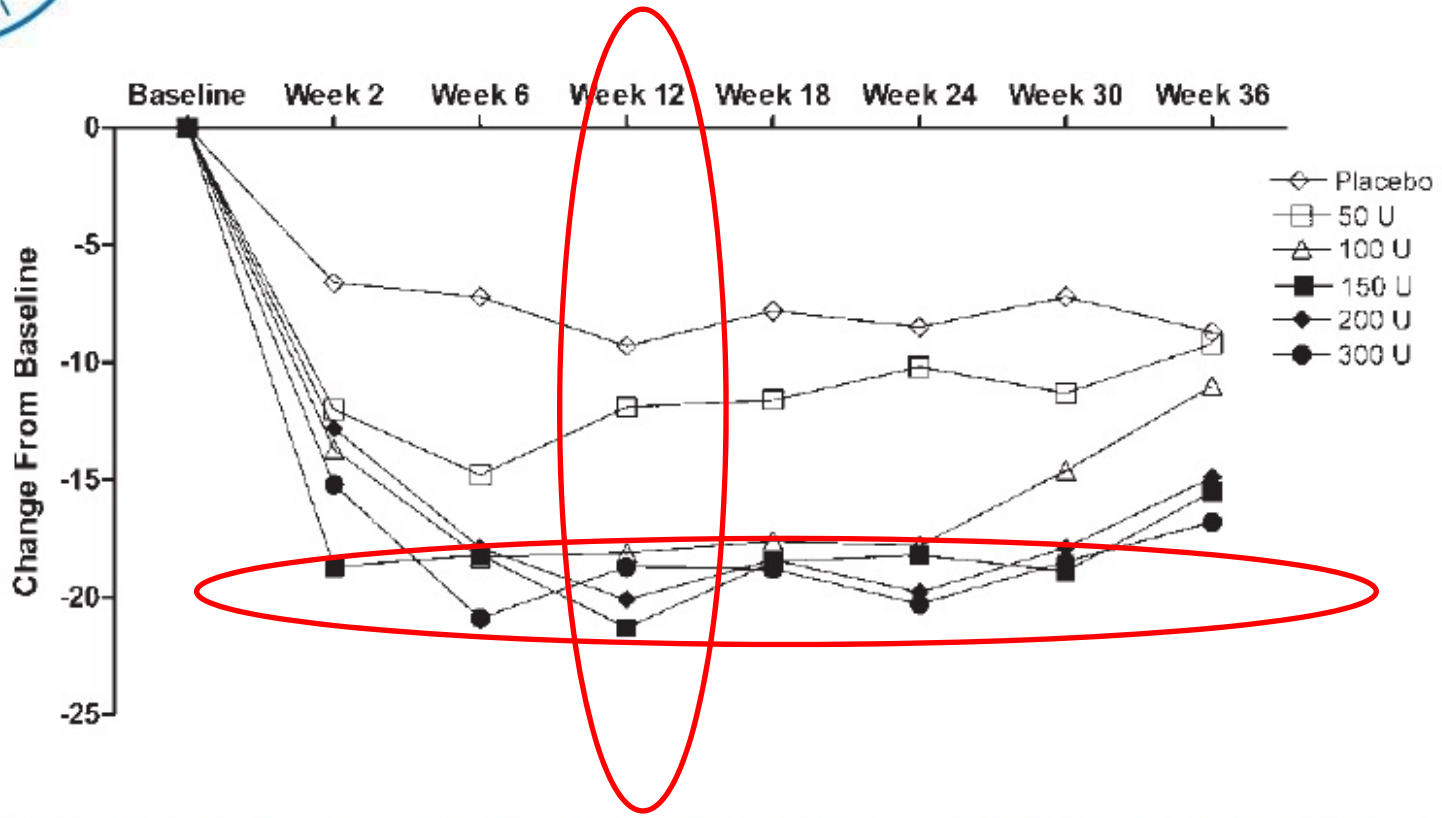


Figure 3. Change from baseline in mean King's Health Questionnaire score (symptoms component) by treatment group.

Dmochowski 2010

Güvenlik

- Üriner enfeksiyon
- Üriner retansiyon
  - TAK ihtiyacı
  - Üretral kateter ihtiyacı
- PVR de artış

Dmochowski 2010

Table *Summary of safety by treatment group (safety population)*

		OnabotulinumtoxinA Dose				
	Placebo	50 U	100 U	150 U	200 U	300 U
No. pts	43	56	55	50	52	55
Total No. AEs (%)	33 (76.7)	44 (78.6)	44 (80.0)	39 (78.0)	44 (84.6)	46 (83.6)
No. treatment related AEs (%)	8 (18.6)	17 (30.4)	20 (36.4)	20 (40.0)	20 (38.5)	22 (40.0)
No. UTIs (%)	7 (16.3)	19 (33.9)	20 (36.4)	22 (44.0)	25 (48.1)	19 (34.5)
No. urinary retention (%)*	1 (2.3)	5 (8.9)	10 (18.2)	14 (28.0)	12 (23.1)	14 (25.5)
No. residual urine/residual urine vol (%)	0 (0.0)	3 (5.4)	2 (3.6)	3 (6.0)	4 (7.7)	2 (3.6)
No. PVR 200 ml or greater (%)	0 (0.0)	7 (12.5)	8 (14.5)	10 (20.0)	15 (28.8)	15 (27.3)
No. PVR related catheterization (%)†	0 (0.0)	3 (5.4)	6 (10.9)	10 (20.0)	11 (21.2)	9 (16.4)
Median days PVR related catheterization (range)†	Not available	30 (5–130)	113 (16–441)	57 (3–245)	179 (35–241)	15 (4–247)

* Definition of urinary retention added into study of PVR 200 ml or greater.
† CIC or indwelling.

Dmochowski 2010

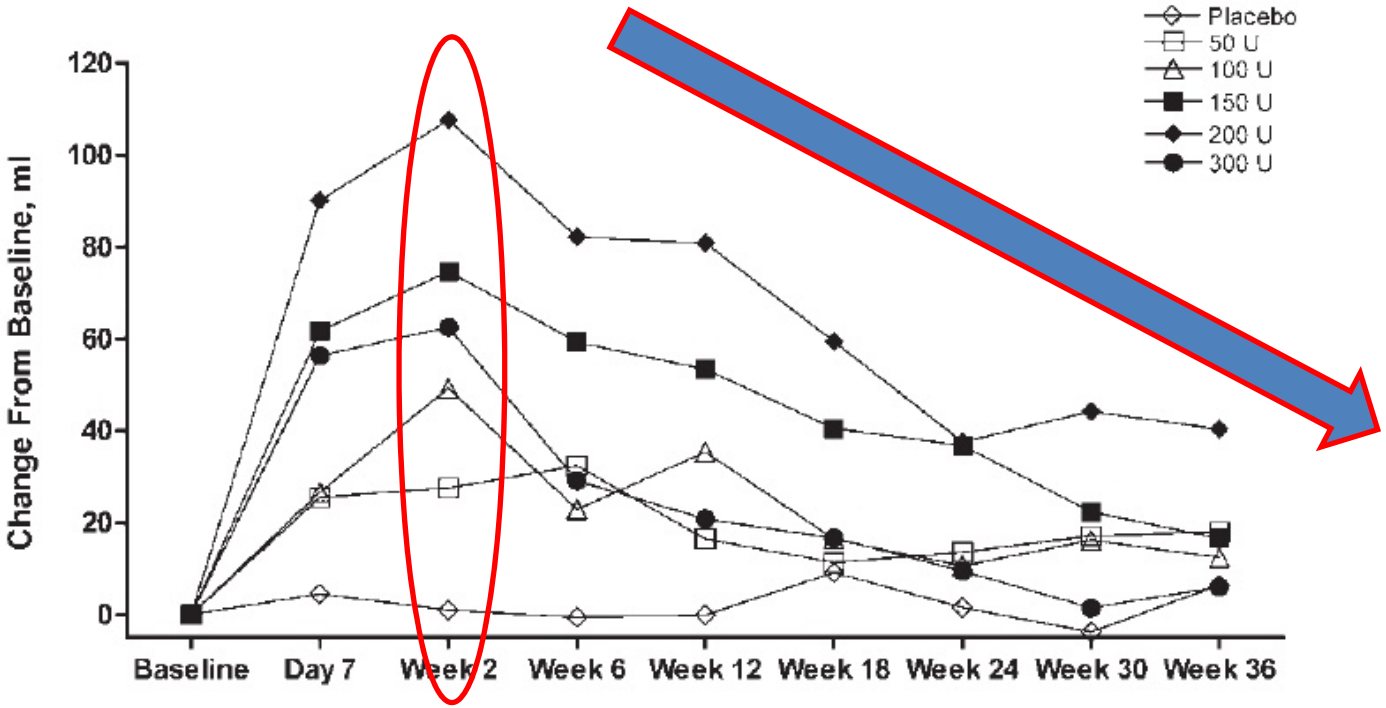
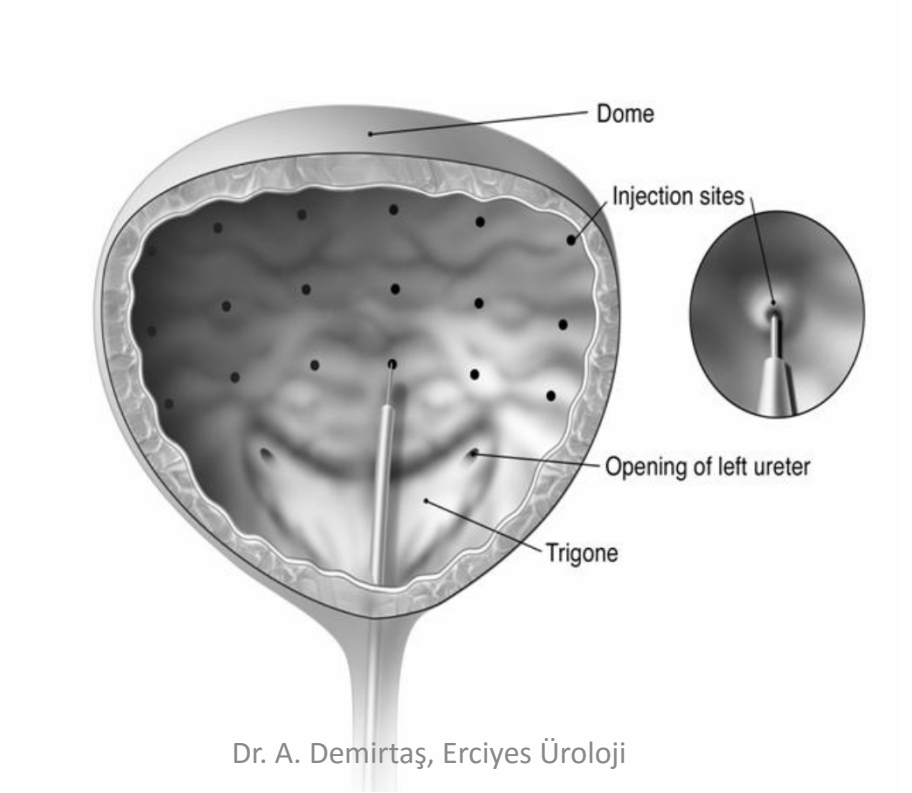


Figure 4. Change from baseline in mean PVR urine volume by treatment group.

Dmochowski 2010

iAAM	NDAA
100 U/10 cc	200 U/30 cc
0.5 cc/20 noktaya	1 cc/30 noktaya
Ort. 6 ayda bir	Ort. 9 ayda bir



Davis 2015, trigon dahil, hariç

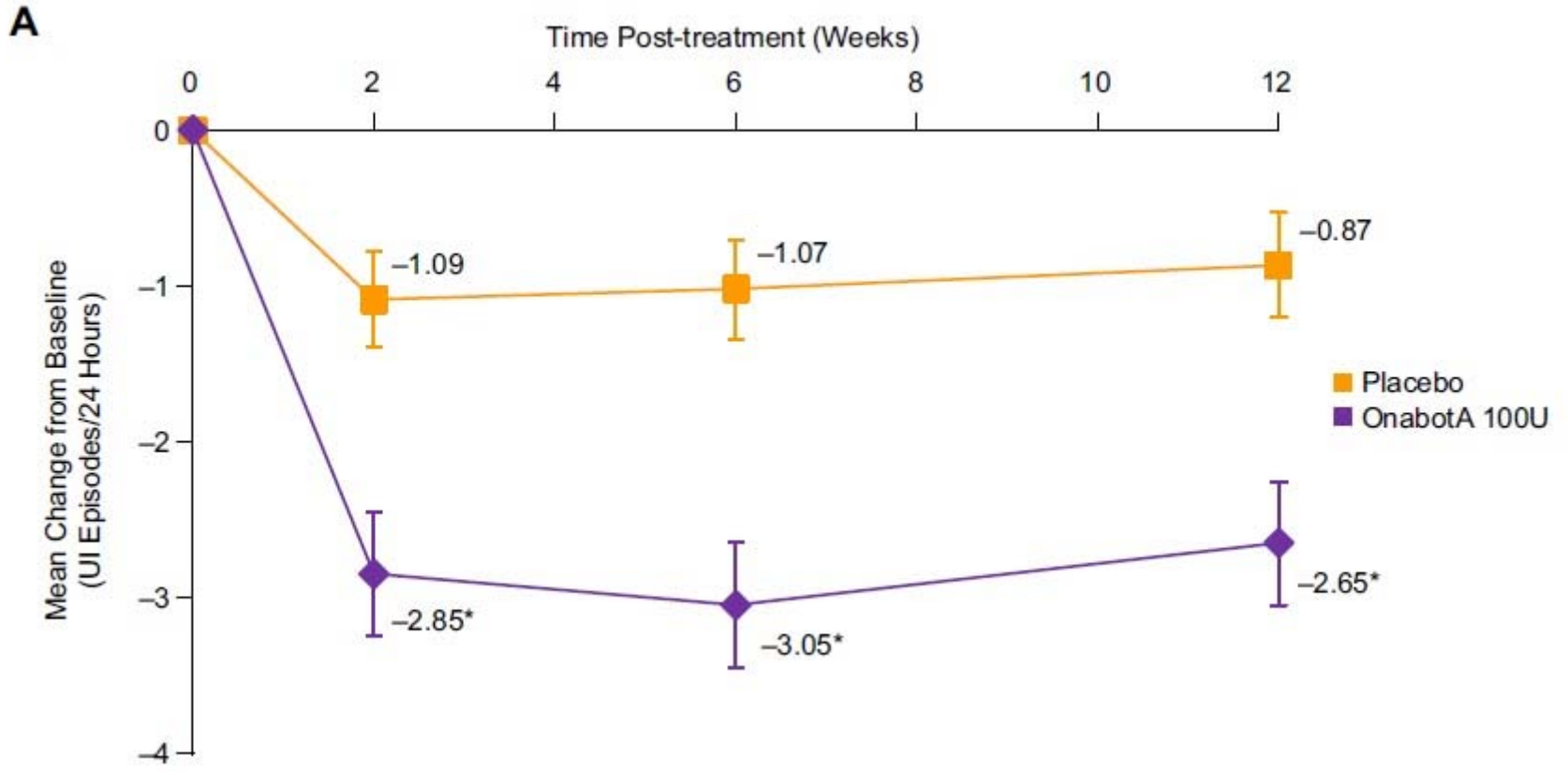
- Faz III, randomize, plasebo kontrollü
- 2009-2011, 557 hasta,
- AAM semptomları 6.7 yıl
- İdrar kaçırma epizotları azalma
- Sıkışma sayısında azalma
- TAK oranı geçici (6 ay) %6.5

Ekinlik

- Primer etki
  - Urge üriner inkontinans
- Sekonder etki
  - İşeme sıklığı azalma
  - Urgency azalma
  - Noktüri azalma
  - İşeme volümümde artış
- Etki 2. hafta başlayıp 12 hafta devam etmiş

Nitti WV., 2013

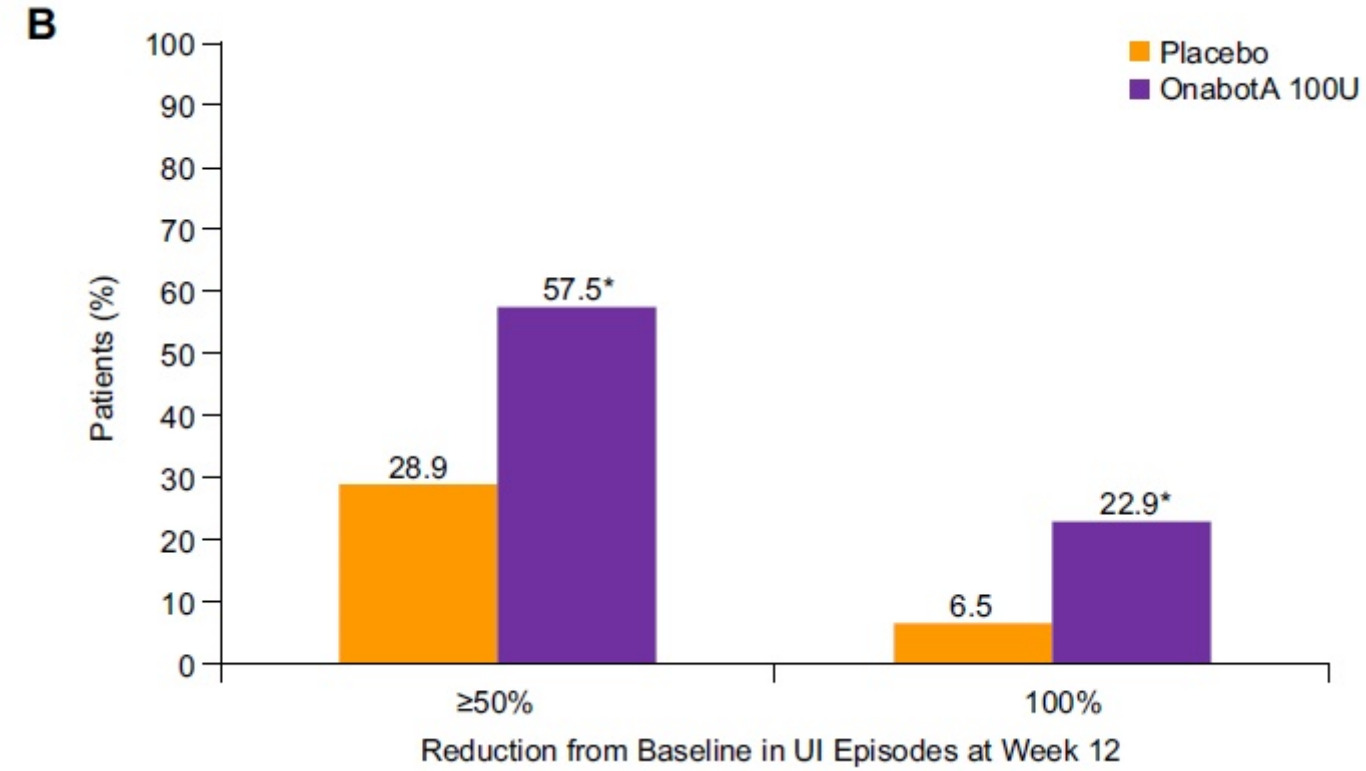
Üriner inkontinans



Botox %47.9, plasebo %12.5

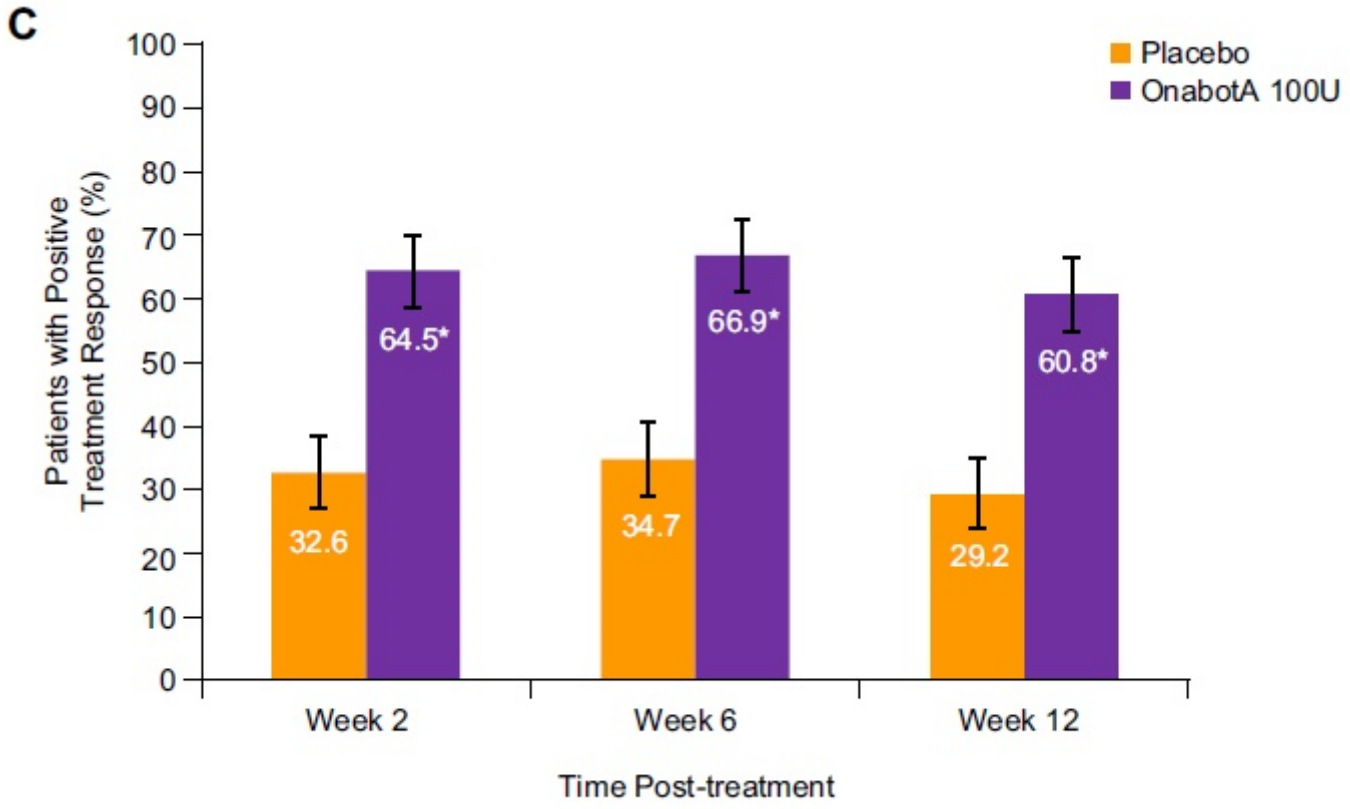
Nitti WV., 2013

Kontinans



Nitti WV., 2013

Tedavi cevabı



Nitti WV., 2013

Güvenlik, yan etki

Table 3. *Key safety parameters in first 12 weeks after treatment 1 and at any time during treatment cycle 1 in safety population*

	No. First 12 Wks (%)		No. Any Time (%)*	
	Placebo	OnabotulinumtoxinA 100 U	Placebo	OnabotulinumtoxinA 100 U
No. pts	272	278	272	278
AE with 5% or greater incidence:				
UTI†	16 (5.9)	43 (15.5)	25 (9.2)	68 (24.5)
Dysuria	26 (9.6)	34 (12.2)	27 (9.9)	40 (14.4)
Bacteriuria	5 (1.8)	14 (5.0)	10 (3.7)	23 (8.3)
Urinary retention‡	1 (0.4)	15 (5.4)	1 (0.4)	16 (5.8)
Serious AE	8 (2.9)	9 (3.2)	16 (5.9)	18 (6.5)
Death	0	0	1 (0.4)	0
PVR (ml):	0		0	
200 or Greater change from baseline		19 (6.8)		24 (8.7)§
200 or Greater		24 (8.6)		31 (11.2)

* Onset between treatment 1 receipt and re-treatment or study exit.

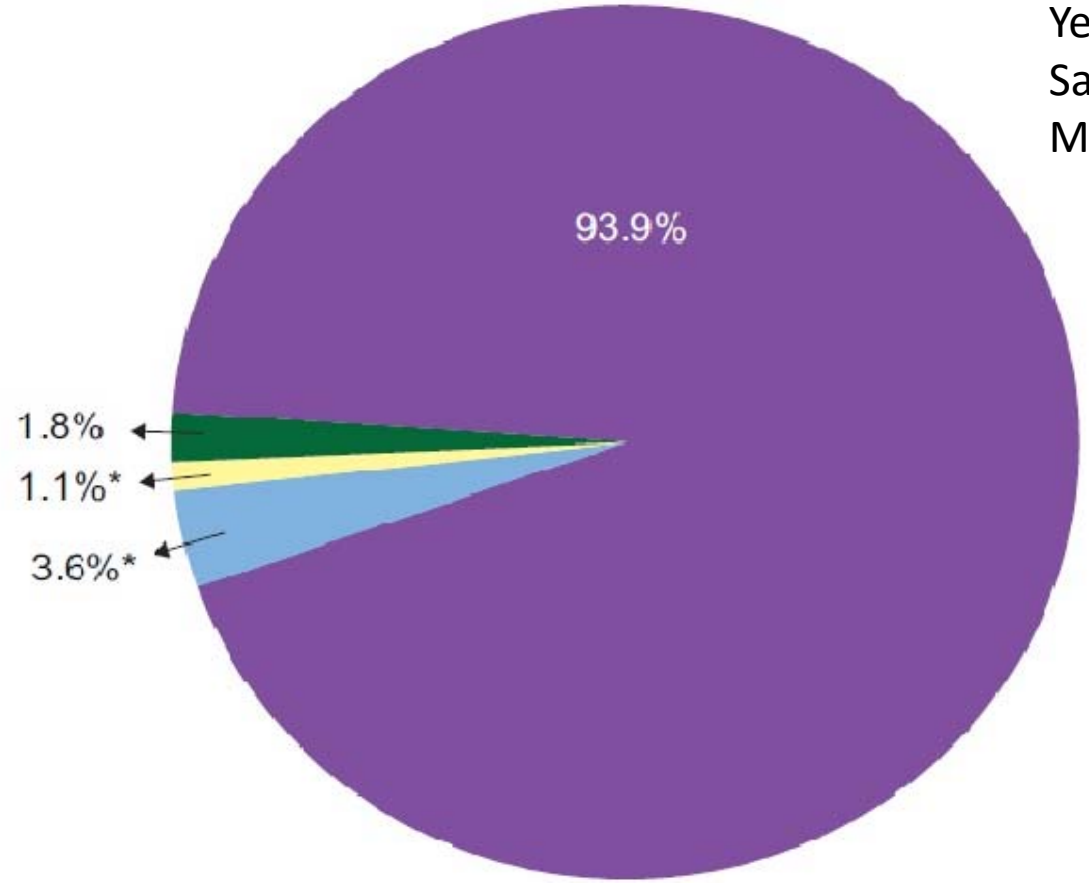
† Positive urine culture with bacteriuria count greater than 10^5 cfu/ml and leukocyturia greater than 5 per high power field.

‡ PVR 200 ml or greater requiring CIC.

§ In 276 patients due to no baseline value in 2.

Nitti WV., 2013

TAK oranı



Yeşil alan 12 haftadan uzun TAK,
Sarı alan 6-12 hafta arası TAK,
Mavi alan 6 haftadan az TAK

Nitti WV., 2013

EUROPEAN UROLOGY 64 (2013) 249–256

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Incontinence

Editorial by Stephan Madersbacher on pp. 257–259 of this issue

OnabotulinumtoxinA 100 U Significantly Improves All Idiopathic Overactive Bladder Symptoms and Quality of Life in Patients with Overactive Bladder and Urinary Incontinence: A Randomised, Double-Blind, Placebo-Controlled Trial

Christopher Chapple [a,], Karl-Dietrich Sievert [b], Scott MacDiarmid [c], Vik Khullar [d], Piotr Radziszewski [e], Christopher Nardo [f], Catherine Thompson [g], Jihao Zhou [f], Cornelia Haag-Molkenteller [f]*

THE JOURNAL of UROLOGY®

Official Journal of the American Urological Association

Uro

Articles & Issues | Collections | Multimedia | News | For Authors | Journal Info | Subscribe | AUA

All Content | Search | Advanced Search

< Previous Article | June 2013 Volume 189, Issue 6, Pages 2186–2193 | Next Article >

OnabotulinumtoxinA for the Treatment of Patients with Overactive Bladder and Urinary Incontinence: Results of a Phase 3, Randomized, Placebo Controlled Trial

Victor W. Nitti†, Roger Dmochowski‡, Sender Herschorn§, Peter Sand¶, Catherine Thompson||, Christopher Nardo||, Xiaohong Yan||, Cornelia Haag-Molkenteller||, EMBARK Study Group

Neurourology and Urodynamics

Neurourology and Urodynamics 33:S26–S31 (2014)

Chapter 5: Clinical Data in Neurogenic Detrusor Overactivity (NDO) and Overactive Bladder (OAB)

Francisco Cruz[1]* and Victor Nitti[2]
[1]Hospital São João, IBMC & Faculty of Medicine do Porto, Porto, Portugal
[2]Department of Urology, New York University School of Medicine, New York, USA

TABLE IV. Clinical and Urodynamic Parameters at Week 12 in the EMBARK Trials (OAB)

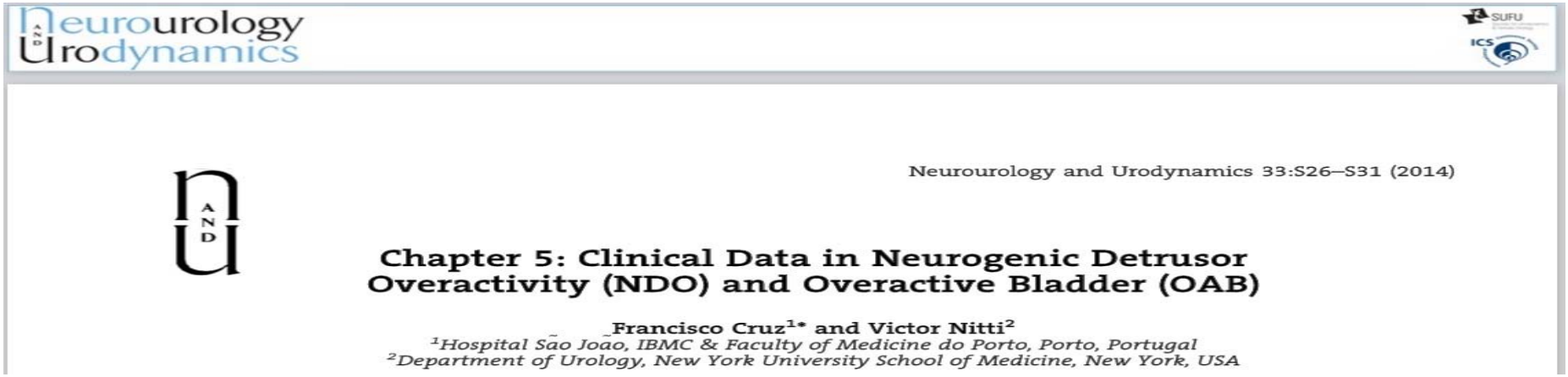
	Nitti et al.[24]		Chapple et al.[23]	
	Placebo (n = 277)	OnabotulinumtoxinA 100 U (n = 280)	Placebo (n = 271)	OnabotulinumtoxinA 100 U (n = 277)
Mean change from baseline in clinical and urodynamic parameters at week 12				
UI episodes/day (co-primary endpoint)	−0.87	−2.65†	−1.03	−2.95†
Micturition episodes/day	−0.91	−2.15†	−0.83	−2.56†
Urgency episodes/day	−1.21	−2.93†	−1.24	−3.67†
Nocturia episodes/day	−0.24	−0.45*	−0.25	−0.54‡
Patients with a positive response on TBS, % (co-primary endpoint)	29.2	60.8†	26.8	62.8†
Mean change in I-QOL score[a]				
Total summary	6.8	21.9†	6.3	23.1†
Avoidance and limiting behavior	7.3	23.9†	6.0	23.5†
Psychological impact	6.1	19.6†	6.5	21.5†
Social embarrassment	7.2	22.6†	6.3	25.0†
Mean change in KHQ multi-item domain score[b]				
Role limitations	−2.4	−24.3†	−5.0	−26.5†
Social limitations	−3.8	−17.3†	−1.3	−16.2†
Physical limitations	−5.4	−20.8†	−5.9	−22.5†
Personal relationships	−1.1	−13.4†	−2.8	−11.7†
Emotions	−5.9	−17.4†	−4.2	−19.6†
Sleep/energy	−5.3	−15.1†	−7.5	−20.1†
Severity/coping measures	−3.3	−19.7†	−3.9	−19.1†

OAB, overactive bladder; UI, urinary incontinence; I-QOL, Incontinence Quality of Life; KHQ, King's Health Questionnaire; TBS, treatment benefit scale.
[a]Higher scores indicate better health-related quality of life (HRQOL); the minimal important difference (MID) is a 10-point increase.
[b]Lower scores indicate better HRQOL; the MID is a 5-point decrease.
*$P \leq 0.05$.
‡$P < 0.01$.
†$P < 0.001$.

Neurourology and Urodynamics DOI 10.1002/nau

Tekrarlayan uygulamalarda

- 345 hasta (1.,2.,3. uygulama)
- Uİ da azalma (-3.07,-3.49,-3.49)
- Pozitif tedavi cevabı (%63.6, 76.9, 77.3)
- Retansiyon, TAK stabil (%4.6, 4.1, 4.7)



Accepted Manuscript

Title: Use of Botulinum Toxin in Urologic Diseases

Author: Christopher J. Chermansky, Michael B. Chancellor

PII: S0090-4295(16)00012-1
DOI: http://dx.doi.org/doi: 10.1016/j.urology.2015.12.049
Reference: URL 19566

To appear in: *Urology*

Received date: 30-9-2015
Accepted date: 30-12-2015

Article in Press

Durable Efficacy and Safety of Long-term OnabotulinumtoxinA Treatment in Patients with Overactive Bladder Syndrome: Final Results of a 3.5 Year Study

Victor W. Nitti, David Ginsberg, Karl-Dietrich Sievert, David Sussman, Sidney Radomski, Peter Sand, Dirk De Ridder, Brenda Jenkins, Andrew Magyar, Christopher Chapple on behalf of the 191622-096 investigators

THE JOURNAL of UROLOGY®

Official Journal of the American Urological Association

- 3.5 yıl, 6 uygulama
- 12. haftada değerlendirme
- UÜİ ataklarında azalma
- Etki kalıcı
- Ortanca etki süresi 7.6 ay
- Hasta memnuniyet oranı %70-90
- Antikor gelişimi yok, respiratuar risk yok,
- Fibrozis yok

Nitti 2015,193;e719-e720

AAM için Sonuçlar

- Doz seçimi için Faz II çalışma, etkinlik güvenlik için iki tane Faz III çalışma (1105 hasta(557+548))
  - (50-300 U) 100 U
  - Uygulamada trigon ve kubbe korunmuş (20 noktaya)
  - Etki 2 haftada başlayıp 12. haftaya kadar devam ediyor
  - Urge üriner inkontinans ataklarında azalma
  - İdrar yapma sıklığında azalma
  - Noktüride azalma
  - Urgency azalma

AAM için Sonuçlar

- İdrar yapma volümünde artma
- PVR de atma
- TAK oranı düşük (%6.1, etki geçici, %1.8 12 hafatadan uzun sürüyor)
- İlk uygulamadan sonra etki 3. ayda azalmaya başlayıp 6-9 aya kadar devam ediyor
- Uzun dönemde tekrarlanabilir bir tedavi

eau

Summary of evidence	LE
A single treatment session of onabotulinum toxin A (100 U) injected in the bladder wall is more effective than placebo at curing and improving UUI and QoL.	1a
There is no evidence that repeated injections of onabotulinum toxin A have reduced efficacy.	3
There is a high risk of increased PVR when injecting elderly frail patients.	3
The risk of bacteruria after onabotulinum toxin A (100 U) injection is high but the clinical significance of this remains uncertain.	1b
Onabotulinum toxin A (100 U) is superior to solifenacin for cure of UUI, but rates of improvement were equivalent.	1b

Recommendations	GR
Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with urgency urinary incontinence refractory to antimuscarinic therapy.	A
Warn patients of the limited duration of response, risk of urinary tract infection and the possible prolonged need to self-catheterise (ensure that they are willing and able to do so).	A

Maliyet

- 188-330TL İLAÇ BEDELİ
- Yatak ücreti, anestezi maliyeti
- Kolay tekrarlanabilir işlem sistoskopla yapılıyor
- Poliklinik şartlarında da yapılabilir
- Öğrenimi kolay
- Radyasyon yok

TEŞEKKÜRLER