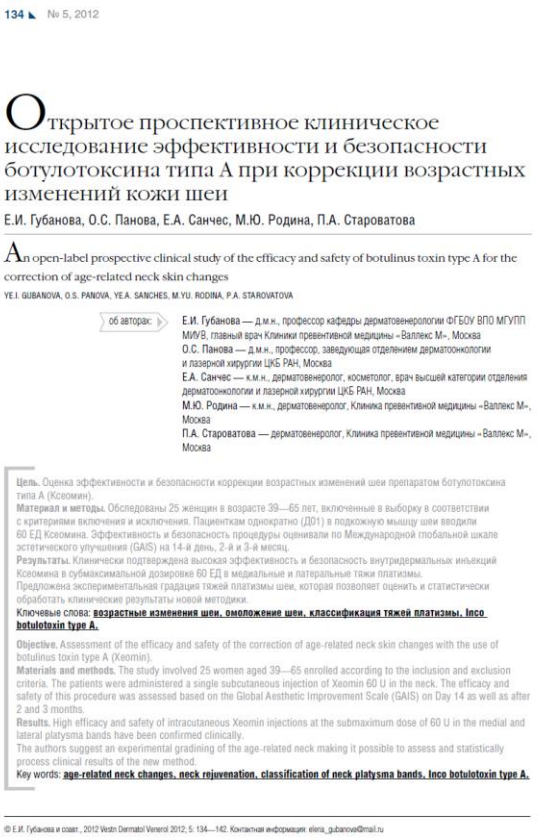
Основательная доказательная база: у Ксеомина более 100 публикаций основанных на более чем 76 масштабных клинических исследованиях (2005-2016 гг)

	Сравнительные		Несравнительные
	Ботокс	Диспорт	
Общее количество	**19**	**8**	**49**
Безопасность	*19*	*8*	*49*
Длительность эффекта	*19*	*8*	*49*
Время наступления эффекта	*4*	*4*	*NA*
Эквивалентность препаратов в зависимости от дозы	*19*	*8*	*NA*
Диффузия препарата	*3*	*3*	*8*
Иммуногенность	*2*	*2*	*11*

План

	ОБЪЕКТИВНЫЕ ДОКАЗАТЕЛЬСТВА БЕЗОПАСНОСТИ КСЕОМИНА
1	Безопасность при применении в нижней трети лица и области вокруг глаз
2	Безопасность при применении гибких интервалов
3	Безопасность при применении суммарно высоких доз
	ОБЪЕКТИВНЫЕ ДОКАЗАТЕЛЬСТВА ЭФФЕКТИВНОСТИ КСЕОМИНА
4	Низкий риск развития иммуногенности при применении высоких доз
5	Быстрое начало эффекта
6	Длительность сохранения эффекта
7	Высокая удовлетворенность пациентов

Открытое проспективное клиническое исследование без группы сравнения оценки эффективности и безопасности Ботулотоксина типа А (Xeomin) для лечения возрастных изменений кожи шеи (коррекции тяжей платизмы)



Открытое проспективное клиническое исследование эффективности и безопасности ботулотоксина типа А при коррекции возрастных изменений кожи шеи

Е.И. Губанова, О.С. Панова, Е.А. Санчес, М.Ю. Родина, П.А. Староватова

An open-label prospective clinical study of the efficacy and safety of botulinus toxin type A for the correction of age-related neck skin changes

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Цель. Оценка эффективности и безопасности коррекции возрастных изменений шеи препаратом ботулотоксина типа А (Ксеомин).
Материал и методы. Обследованы 25 женщин в возрасте 39—65 лет, включенные в выборку в соответствии с критериями включения и исключения. Пациенткам однократно (Д01) в подкожную мышцу шеи вводили 60 ЕД Ксеомина. Эффективность и безопасность процедуры оценивали по Международной глобальной шкале эстетического улучшения (GAIS) на 14-й день, 2-й и 3-й месяц.
Результаты. Клинически подтверждена высокая эффективность и безопасность внутридермальных инъекций Ксеомина в субмаксимальной дозировке 60 ЕД в медиальные и латеральные тяжи платизмы.
Предложена экспериментальная градация тяжей платизмы шеи, которая позволяет оценить и статистически обработать клинические результаты новой методики.
Ключевые слова: **возрастные изменения шеи, омоложение шеи, классификация тяжей платизмы, Inco botulotoxin type A.**

Objective. Assessment of the efficacy and safety of the correction of age-related neck skin changes with the use of botulinus toxin type A (Xeomin).
Materials and methods. The study involved 25 women aged 39—65 enrolled according to the inclusion and exclusion criteria. The patients were administered a single subcutaneous injection of Xeomin 60 U in the neck. The efficacy and safety of this procedure was assessed based on the Global Aesthetic Improvement Scale (GAIS) on Day 14 as well as after 2 and 3 months.
Results. High efficacy and safety of intracutaneous Xeomin injections at the submaximum dose of 60 U in the medial and lateral platysma bands have been confirmed clinically.
The authors suggest an experimental grading of the age-related neck making it possible to assess and statistically process clinical results of the new method.
Key words: **age-related neck changes, neck rejuvenation, classification of neck platysma bands, Inco botulotoxin type A.**

© Е.И. Губанова и соавт., 2012 Vestn Dermatol Venerol 2012; 5: 134—142. Контактная информация: elena_gubanova@mail.ru

Дизайн исследования

Цель: Оценить безопасность и эффективность инъекций Ксеомина для коррекции тяжей платизмы

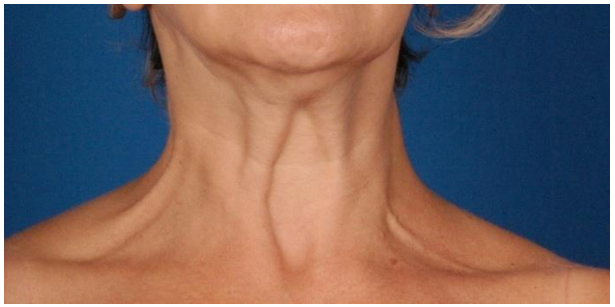
Пациенты с выраженностью тяжей платизмы 2-4 стадии согласно шкале Merz
- N=28
- Длительность: 12-недель

Инкоботулинумтоксин А
60 ЕД однократно в подкожную мышцу шеи

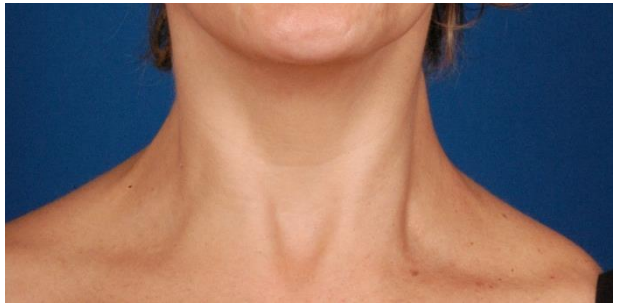
Оценка результатов
- **на 14 день**
- **через 2 месяца**
- **через 3 месяца**

Е.И. Губанова с соавт., 2012 Вестн дермат.венерол. 2012; 5: 134-142

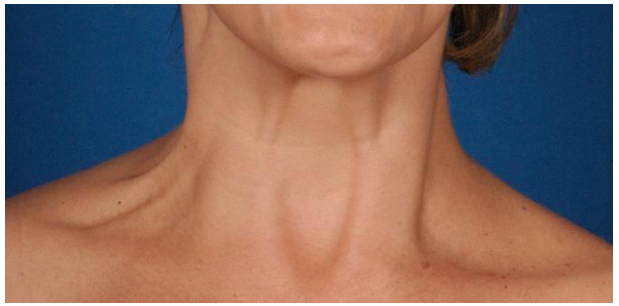
Сохранение эффекта коррекции по сравнению с начальным клиническим результатом



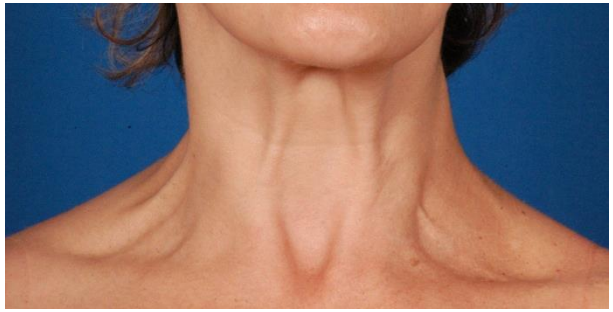
Д01



Д14



М02



М03

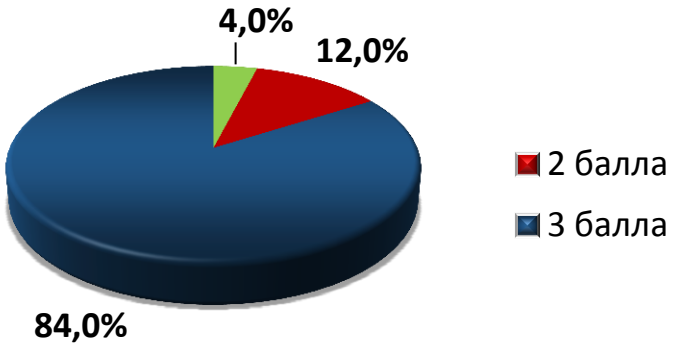
Е.И. Губанова с соавт., 2012 Вестн дермат.венерол. 2012; 5: 134-142

Результаты исследования – оценка по шкале GAIS пациентом

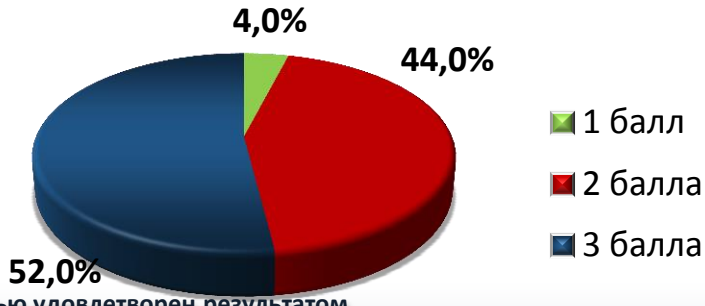
Среднее значение по шкале GAIS: оценка пациентом – 2,7 балла

Среднее значение по шкале GAIS: оценка врачом – 2,9 балла

Д14 2,72±0,84



М03 2,48±0,59



Эффективность

- Улучшение состояния кожи шеи по GAIS наблюдалось у 100% женщин согласно оценке врача и пациента.
- Длительность эффекта составляет более 3 месяцев с сохранностью эффекта в среднем 86,3% к 3-му месяцу после инъекции.

3 балла – Полностью удовлетворен результатом

2 балла – Удовлетворен результатом, но хотелось бы немного улучшить

1 балл – Улучшение незначительное, желательна дополнительная коррекция

Е.И. Губанова с соавт., 2012 Вестн дермат.венерол. 2012; 5: 134-142

Безопасность

Применение КСЕОМИНА в нижней трети лица не вызывает серьезных побочных явлений

- Общие нежелательные явления:
  - дисфагия, слабость мышц шеи наблюдались у 3 пациенток, были связаны со схемой введения препарата и самостоятельно регрессировали в течение 2-4 недель.
- Эстетические нежелательные явления:
  - появление компенсаторных тяжей, усиление дополнительных тяжей, дряблость кожи под подбородочной области
- Не было зафиксировано серьезных побочных эффектов

Все наблюдаемые нежелательные эффекты характеризовались легкой или среднетяжелой степенью

Е.И. Губанова с соавт., 2012 Вестн дермат.венерол. 2012; 5: 134-142

Применение Инкоботулотоксина А для коррекции тяжей платизмы: несравнительное исследование для подтверждения клинической эффективности

IncobotulinumtoxinA for the Treatment of Platysmal Bands: A Single-Arm, Prospective Proof-of-Concept Clinical Study

Welf Prager, MD,* Eva K. Bee, MD,† Isabel Havermann, MD,* and Ina Zschocke, PhD‡

BACKGROUND IncobotulinumtoxinA improves the appearance of facial rhytides and the aging neck.

OBJECTIVE To investigate the efficacy, safety, and subject satisfaction of incobotulinumtoxinA for platysmal band treatment.

METHODS Subjects (n = 23) with 2 to 4 platysmal bands (scoring ≥1 on a newly validated 5-point assessment scale) were enrolled. IncobotulinumtoxinA (15 U) was administered to each band. Assessments, using the 5-point scale, occurred at 6 posttreatment visits over 5 months. Adverse events were recorded and subjects self-assessed the appearance of their platysmal bands versus baseline.

RESULTS At maximum tension, a response (≥1-point improvement from baseline score) was observed in 65.2% of subjects 3 (±1) days posttreatment, rising to 100% on Day 8 (±1). The change from baseline in the mean score was significant at each time point, including the final visit (Weeks 20–21). Response rates were higher at maximum tension than at rest. The peak effect occurred later at rest than at maximum tension. No serious adverse event occurred. At maximum tension, 69.6%, 73.9%, and 68.2% of subjects rated their platysmal bands as "improved" or "markedly improved" at Visits 2, 3, and 4, respectively.

CONCLUSION IncobotulinumtoxinA is an effective and well-tolerated treatment for platysmal bands, with a rapid onset and long duration of effect.

W. Prager and E. K. Bee are consultants of Merz. The other authors have indicated no significant interest with commercial supporters.

Дизайн исследования

Цель: Оценить эффективность и безопасность применения инкоботулотоксина А для тяжей платизмы, а также определить степень удовлетворённости пациентов лечением

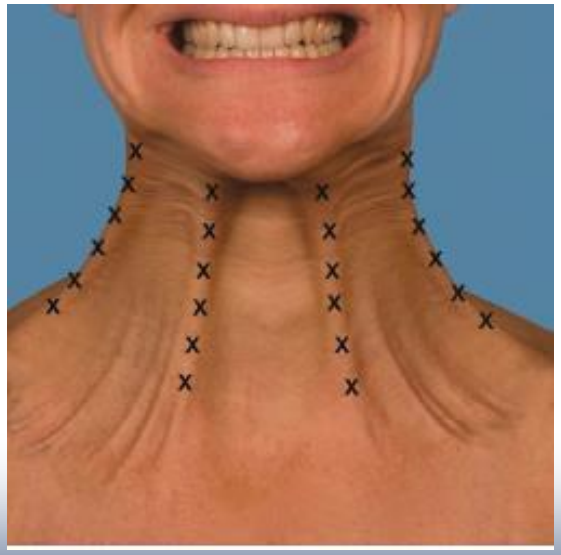
Пациенты с выраженностью тяжей платизмы 2-4 стадии согласно шкале Merz

- N=23
- Длительность: 5-месяцев

Инкоботулотоксин А
15 ЕД в каждый из тяжей платизмы
Общая доза 30-60 ЕД в зависимости от выраженности тяжей

Оценка результатов

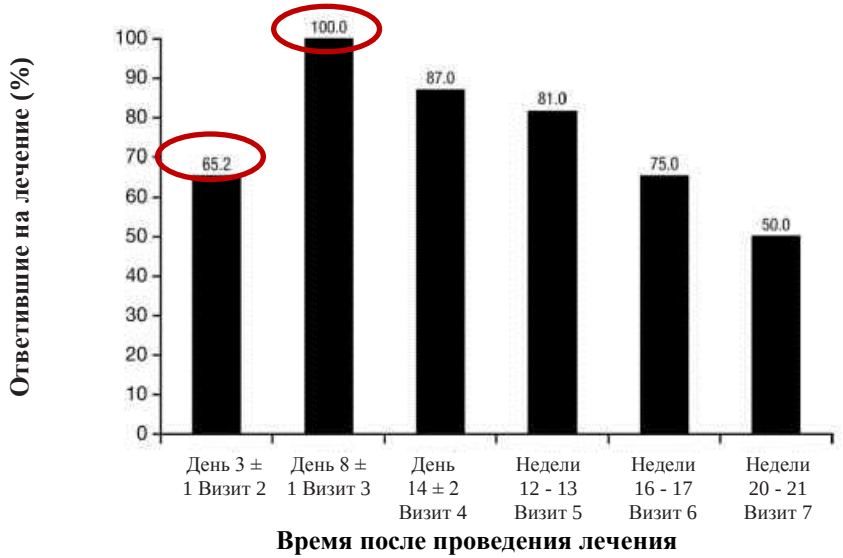
- **6 визитов в течение 5 месяцев**



W. Prager et al,Dermatol Surg 2015;41:S88-S92

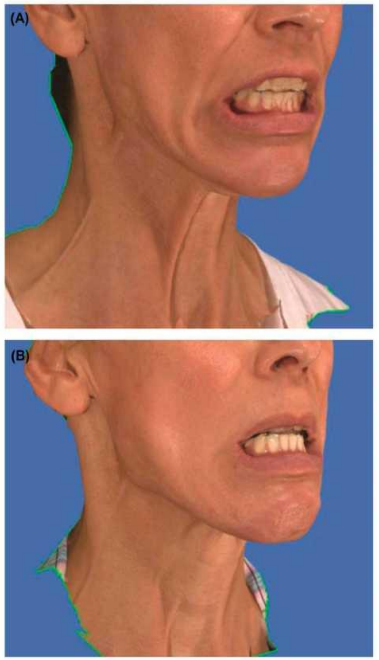
При максимальном напряжении частота ответов на лечение достигала 100% к 3-му визиту (8-й день).

Частота ответов по оценке независимого эксперта при максимальном напряжении с течением времени*.



*согласно 5-балльной шкале компании «Мерц» для оценки тяжей платизмы

Клинические фотографии пациентов с тяжами платизмы в состоянии максимального напряжения



(A) перед проведением лечения и через 2 недели (B) после введения инкоботулотоксина

Безопасность

НЕ было зафиксировано серьезных побочных явлений на протяжении всего исследования

Эффективность

При максимальном напряжении частота ответов на лечение достигала 100% к 3-му визиту (8-й день).

W. Prager et al, Dermatol Surg 2015;41:S88-S92

Оценка переносимости и эффективности использования гибких интервалов введения Инкоботулотоксина А у пациентов с цервикальной дистонией или блефароспазмом

НЕВРОЛОГИЯ

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Efficacy and safety of incobotulinumtoxinA (NT 201, XEOMIN®, botulinum neurotoxin type A, without accessory proteins) in patients with cervical dystonia☆

Cynthia L. Comella *, Joseph Jankovic, Daniel D. Truong, Angelika Hanschmann, Susanne Grafe on behalf of the U.S. XEOMIN Cervical Dystonia Study Group [1]

Merz Pharmaceuticals GmbH, Frankfurt, Germany

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ABSTRACT

Objective: IncobotulinumtoxinA differs from available formulations in that it does not have accessory proteins. IncobotulinumtoxinA has previously shown non-inferiority to onabotulinumtoxinA for the treatment of CD with a 1:1 dosing regimen. The objective of this study was to compare the safety and efficacy of incobotulinumtoxinA (120 U, 240 U; Merz Pharmaceuticals) to placebo in subjects with cervical dystonia (CD).
Methods: This was a prospective, double-blind, randomized, placebo-controlled, multicenter clinical trial in botulinum toxin-treated or toxin-naïve CD patients. The primary outcome measure was change from baseline to Week 4 on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Total score. Adverse events (AEs) also were evaluated.
Results: Participants (N = 233) were mostly women (66%), a mean of 52.8 years old, who had CD for a mean of 51.9 months. Of those, 39% were toxin-naïve. IncobotulinumtoxinA significantly improved TWSTRS-Total scores from baseline to Week 4 compared to placebo (placebo = −2.2; 120 U = −9.9, and 240 U = −10.9; 240 U vs. placebo $p<0.001$ and 120 U vs. placebo $p<0.001$). This effect persisted through to the end of the study. The most frequently reported AEs in the incobotulinumtoxinA groups were dysphagia, neck pain, and muscular weakness which were generally mild. Interpretation: IncobotulinumtoxinA (at doses of 120 U or 240 U) is a safe and effective treatment for CD in previously-treated as well as toxin-naïve subjects.
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1. Introduction

Cervical dystonia (CD) is a focal dystonia that causes abnormal postures of the head, neck and shoulders. Class A evidence has established botulinum toxin treatment as an effective means to control the symptoms of CD [1]. IncobotulinumtoxinA (marketed as XEOMIN® in the US, Canada and Europe, Merz Pharmaceuticals, GmbH, Frankfurt) is a botulinum toxin serotype A that differs from other available botulinum toxin formulations in that the botulinum toxin complex is purified from the culture supernatant and then the active ingredient is separated from the proteins (hemagglutinins and non-hemagglutinins) through a series of steps yielding the active neurotoxin with molecular weight of 150 kDa, without accessory proteins [2]. Whether the absence of accessory proteins confers unique qualities in the therapeutic use of botulinum toxin has not been established. The incobotulinumtoxinA formulation contains only the active portion of the clostridial protein per vial [3,4] and has long-term stability at room temperature (up to 4 years) [5]. Non-inferiority studies in patients with blepharospasm and CD have shown similar effects of onabotulinumtoxinA and incobotulinumtoxinA [6,7].

The specific aim of this study was to evaluate symptom improvement and tolerability associated with a single injection of incobotulinumtoxinA compared to placebo.

2. Methods

This was a prospective, multicenter, double-blind, randomized, placebo-controlled study conducted at 37 sites in the US. The respective Institutional Review Boards approved the study protocol and informed consent process. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and is consistent with Good Clinical Practice and the applicable regulatory requirements. Prior to screening, all subjects provided written informed consent. The study was registered with clinicaltrials.gov (www.clinicaltrials.gov) [Identification number: NCT00407030].

2.1. Subjects

The study was conducted between July, 2006 and March, 2008. Eligible subjects were men or women between the ages of 18 and

☆ Sponsored by Merz Pharmaceuticals GmbH, Frankfurt.

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E-mail address: Cynthia_L_Comella@rush.edu (C.L. Comella).
[1] U.S. XEOMIN Cervical Dystonia Study Group: See Appendix 1 for list of Investigators Sponsored by Merz Pharmaceuticals GmbH, Frankfurt.

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IncobotulinumtoxinA (Xeomin®) injected for blepharospasm or cervical dystonia according to patient needs is well tolerated

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IncobotulinumtoxinA
Xeomin®
Patient satisfaction

ABSTRACT

Typically, botulinum toxin injections for blepharospasm or cervical dystonia (CD) are administered at approximately 3-month intervals, reflecting concerns that shorter intervals might increase the risk of adverse events (AEs) and development of neutralizing antibodies. These post-hoc analyses investigated flexible incobotulinumtoxinA (Xeomin®) injection intervals (6–20 weeks) in patients with blepharospasm or CD. Patients received up to 6 injections at intervals ≥6 weeks, as determined by physician assessment upon patient request. The blepharospasm study permitted flexible doses (≤50 U/eye). The CD study employed fixed dosing using incobotulinumtoxinA 120 U, 240 U, or placebo for the first treatment followed by subsequent randomization to 120 U or 240 U for the extension period. Standard safety assessments were performed. Intervals <12 weeks were employed in 207 of 461 (44.9%) treatment cycles for blepharospasm and in 369 of 821 (44.9%) treatment cycles for CD. The most frequent AEs were eyelid ptosis and dry eyes in patients treated for blepharospasm, and dysphagia and neck pain in patients with CD. AE frequency and severity were similar for intervals <12 weeks and ≥12 weeks in both studies. In conclusion, repeated incobotulinumtoxinA injections employing flexible intervals (6–20 weeks) per patients' needs were well tolerated. No additional safety concerns were observed with <12-week intervals compared with ≥12-week intervals.
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1. Introduction

Repeated intramuscular injections of botulinum toxin are the recommended first-line treatment for focal dystonias, including blepharospasm and cervical dystonia (CD) [1–3].

IncobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH, Frankfurt, Germany; also known as NT 201), a purified botulinum toxin type A formulation free from complexing (or accessory) proteins [4], has been shown to be effective and well tolerated in pivotal Phase III clinical studies in blepharospasm [5,6] and CD [7,8]. In the CD study, subgroup analyses confirmed that incobotulinumtoxinA efficacy and tolerability were similar for patients who were naïve to botulinum toxin treatment and those who had previously received treatment with onabotulinumtoxinA (Botox®, Allergan Inc., Irvine, CA, USA) [9]. The effectiveness of incobotulinumtoxinA in treating CD has been further confirmed in a prospective, long-term, open-label Phase IV study [10]. Further pivotal, randomized, parallel-group head-to-head studies have demonstrated that, at a clinical conversion 1 U:1 U dose ratio, incobotulinumtoxinA and onabotulinumtoxinA showed comparable efficacy and adverse-event (AE) profiles when used to treat blepharospasm [11,12] or CD [13].

Current product labeling of botulinum toxin type A formulations licensed for the treatment of blepharospasm and CD in the USA and Europe recommends injection intervals of at least 3 months or 12 weeks [14–18], with the exception of European labeling for incobotulinumtoxinA, which recommends a minimum treatment interval of 12 weeks for blepharospasm and 10 weeks for CD [19].

The recommended minimum interval of 12 weeks is largely based on a retrospective chart review of patients with CD who received treatment with the early botulinum toxin formulation of onabotulinumtoxinA [20]. However, for many patients with CD, the duration of botulinum toxin treatment effect is less than 12 weeks [21]. Moreover, a recent patient survey revealed that many patients who receive botulinum toxin type A for the treatment of CD would prefer more frequent injections than the currently recommended 12-week inter-dose interval permits [22].

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http://dx.doi.org/10.1016/j.jns.2014.08.004
0022-510X/© 2014 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

Comella Clet al., J Neurol Sci. 2011 Sep 15;308(1-2):103-9
Evidente et al, J Neurol Sci. 2014 Nov 15;346(1-2):116-20

Гибкие интервалы при цервикальной дистонии исходя из потребностей пациентов

НЕВРОЛОГИЯ

Цель: оценить безопасность и эффективность Инкоботулотоксина А при повторяющимся применении с гибкими интервалами у пациентов с цервикальной дистонией

Основной период N=233

Однократная инъекция КСЕОМИН/ПЛАЦЕБО

1. КСЕОМИН 120 ЕД (N=78)
2. КСЕОМИН 240ЕД (N81)
3. ПЛАЦЕБО (N=74)

Повторная рандомизация через ≥8 недель после инъекции

Открытый период N=214

Несколько циклов инъекций КСЕОМИНа (но не более 6)

1. КСЕОМИН 120 ЕД
2. КСЕОМИН 240ЕД

Интервалы между инъекциями - по необходимости, но не менее 6 недель

1. **Безопасность**
2. **Оценка тяжести проявлений ЦД по шкале TWSTRS**

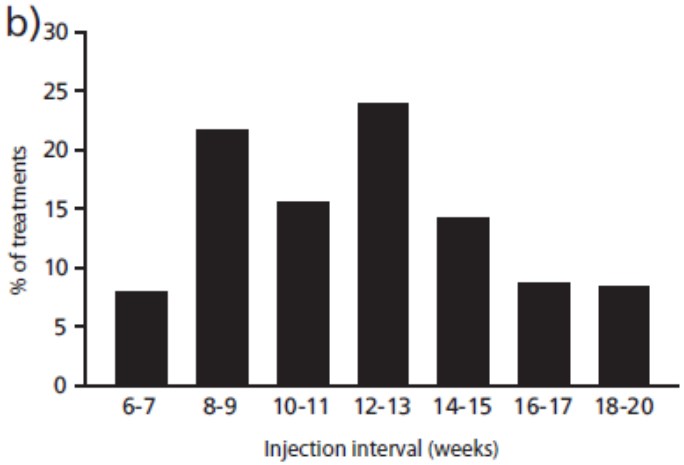
Comella Clet al., J Neurol Sci. 2011 Sep 15;308(1-2):103-9
Evidente et al, J Neurol Sci. 2014 Nov 15;346(1-2):116-20

КСЕОМИН в дозах 120 ЕД и 240 ЕД хорошо переносится пациентами независимо от интервала между инъекциями

НЯ/Интервалы между инъекциями	6-7	8-9	10-11	12-13	14-15	16-17	18-20
Дисфагия	3,1%	5,6%	8,7%	6,1%	7,8%	8,5%	10,1%
Мышечная слабость	1,5%	2,8%	3,1%	2,6%	2,6%	7,0%	0
Боль в области шеи	3,1%	4,5%	4,7%	3,6%	4,3%	5,6%	7,2%
Боль в месте инъекции	1,5%	5,6%	3,1%	2,6%	2,6%	2,8%	1,4%

В 44,9 % случаях интервалы между инъекциями были менее **12 недель**

В 29,5% случаях интервал между введениями был менее **10 недель**



При применении КСЕОМИНА все побочные явления были легкой степени выраженности

Безопасность

Частота возникновения НЯ при повторных сеансах не увеличивается
Нет различий по показаниям НЯ между группами с разными интервалами между инъекциями

Эффективность

Повторяющееся применение фиксированных доз КСЕОМИНА (120 ЕД или 240 ЕД) с гибкими интервалами между инъекциями исходя из потребностей пациентов стабильно облегчало симптомы ЦД

Comella Clet al., J Neurol Sci. 2011 Sep 15;308(1-2):103-9
Evidente et al, J Neurol Sci. 2014 Nov 15;346(1-2):116-20

Практические рекомендации по лечению цервикальной дистонии ботулиническим токсином: консенсусные положения

J Neurol (2015) 262:2201–2213
DOI 10.1007/s00415-015-7703-x

REVIEW

Practical guidance for CD management involving treatment of botulinum toxin: a consensus statement

Alberto Albanese[1] · Giovanni Abbruzzese[2] · Dirk Dressler[3] · Wojciech Duzynski[4] · Svetlana Khatkova[5] · Maria Jose Marti[6] · Pablo Mir[7,8] · Cesare Montecucco[9] · Elena Moro[10] · Michaela Pinter[11] · Maja Relja[12] · Emmanuel Roze[13,14] · Inger Marie Skogseid[15] · Sofiya Timerbaeva[16] · Charalampos Tzoulis[17,18]

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Abstract Cervical dystonia is a neurological movement disorder causing abnormal posture of the head. It may be accompanied by involuntary movements which are sometimes tremulous. The condition has marked effects on patients' self-image, and adversely affects quality of life, social relationships and employment. Botulinum neurotoxin (BoNT) is the treatment of choice for CD and its efficacy and safety have been extensively studied in clinical trials. However, current guidelines do not provide enough practical information for physician
treatment in a real-life s
physicians may have dif
cessful treatment outcom
international group of ex
BoNT treatment, met to r
extensive clinical experi
about treatment of CD w
were considered: the plac

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Zagreb, University of Zag
Croatia

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UPMC Univ Paris 06 UM
la Moelle épinière, ICM,

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University Hospital, Riks

[16] Department of Neurogenetics, Research Center of Neurology,

- Интервал в 12 недель между инъекциями не оправдан
- Повторные инъекции безопасны
- Выбор доз и временного интервала между инъекциями следует корректировать в соответствии с состоянием пациента
- Клинические данные указывают на то, что индивидуально подобранные интервалы между инъекциями могут обеспечивать лучший эффект лечения пациентов

Доказана безопасность Ксеомина в максимальной дозе 800 ЕД (Merz TOWER trial)

Цель: оценить безопасность и эффективность Инкоботулотоксина А у пациентов с постинсультной спастичностью верхних и нижних конечностей

Пациенты с постинсультной спастичностью нижних и верхних конечностей

- N= 155
- Длительность: 48 недель

3 цикла инъекций Инкоботулотоксина А С постепенным увеличением дозы от 400 ЕД- 600 ЕД- до 800 ЕД

Оценка результатов
Через 1, 2, 4, 8 и 12 недель после каждой инъекции

Цикл 1 (12-16 недель) → **Общая доза 400 ЕД**

Цикл 2 (12-16 недель) → **Общая доза 600 ЕД**

Цикл 3 (12-16 недель) → **Общая доза 800 ЕД**

D. Bensmail et al, TOWER: Design and results of an open-label incobotulinumtoxinA dose-titration study (up to 800 U) in upper and lower limb spasticity, Annals of Physical and Rehabilitation Medicine Vol 58, September 2015, Pages e78

Введение Инкоботулотоксина в дозе до 800 ЕД характеризуется хорошей переносимостью и высокой эффективностью

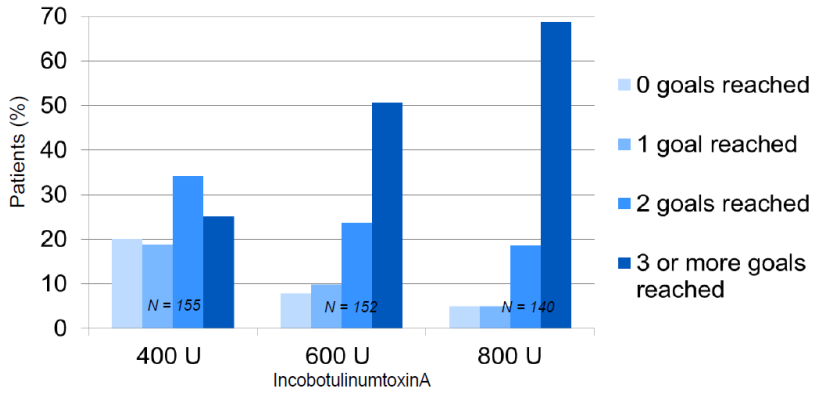
Безопасность

- **НЯ, связанные с терапией:**
  - 400 ЕД: 5.3%
  - 600 ЕД: 2.9%
  - 800 ЕД: 2.6%
- **Переносимость была оценена исследователями как хорошая и очень хорошая**

Не было серьезных НЯ, связанных с инъекцией Ксеомина, которые привели бы к исключению пациентов из исследования

Эффективность

- Число достижения эффекта лечения основного заболевания повышается с увеличением дозы (400ЕД – 600ЕД – 800ЕД)
- Не наблюдали отсутствие ответа на введение Ксеомина из-за развития нечувствительности к ботулотоксину



Не наблюдали отсутствие ответа на введение Ксеомина из-за развития нечувствительности к ботулотоксину

D. Bensmail et al, TOWER: Design and results of an open-label incobotulinumtoxinA dose-titration study (up to 800 U) in upper and lower limb spasticity, Annals of Physical and Rehabilitation Medicine Vol 58, September 2015, Pages e78

Низкий риск развития иммуногенности при применении высоких доз (≥ 400ЕД) КСЕОМИНА

НЕВРОЛОГИЯ

J Neural Transm (2015) 122:327–333
DOI 10.1007/s00702-014-1252-9

PSYCHIATRY AND CLINICAL PSYCHIATRIC STUDIES - ORIGINAL ARTICLE

Safety aspects of incobotulinumtoxinA high-dose therapy

Dirk Dressler · Fereshte Adib Saberi · Katja Kollewe · Christoph Schrader

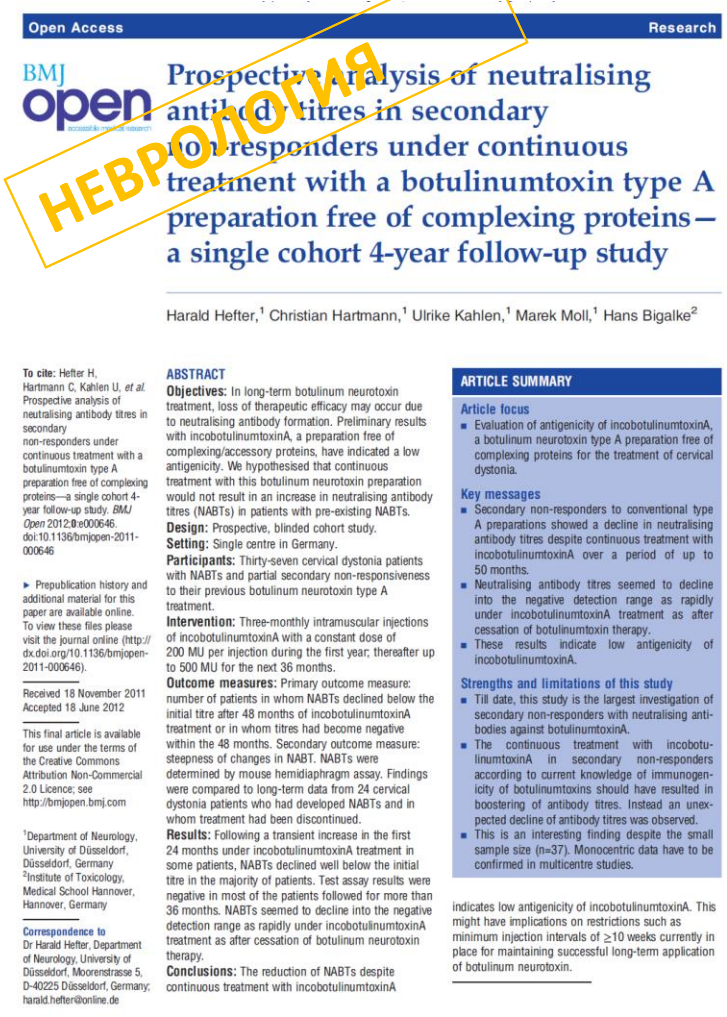
Received: 28 February 2014 / Accepted: 25 May 2014 / Published online: 17 July 2014
© Springer-Verlag Wien 2014

Abstract Botulinum toxin (BT) used for dystonia and spasticity is dosed according to the number of target muscles and the severity of their muscle hyperactivities. With this no other drug is used in a broader dose range than BT. The upper end of this range, however, still needs to be explored. We wanted to do this by a prospective non-interventional study comparing a randomly selected group of dystonia and spasticity patients receiving incobotulinumtoxinA (Xeomin®) high-dose therapy (HD group, $n = 100$, single dose ≥400 MU) to a control group receiving incobotulinumtoxinA regular-dose therapy (RD group, $n = 30$, single dose ≤200 MU). At the measurement point all patients were evaluated for systemic BT toxicity, i.e. systemic motor impairment or systemic autonomic dysfunction. HD group patients (56.1 ± 13.8 years, kinase and lactate dehydrogenase were most likely iatrogenic artefacts. None of the patients developed antibody-induced therapy failure. Xeomin® can be used safely in doses ≥400 MU and up to 1,200 MU without detectable systemic toxicity. This allows expanding the use of BT therapy to patients with more widespread and more severe muscle hyperactivity conditions. Further studies—carefully designed and rigorously monitored—are necessary to explore the threshold dose for clinically detectable systemic toxicity.

Keywords Botulinum toxin · Therapeutic use · High-dose therapy · Safety · Systemic toxicity · Antibody formation

При использовании суммарно высоких доз (400ЕД-1200ЕД) в течение нескольких циклов инъекций (4-37 циклов) НЕ НАБЛЮДАЛИ снижения эффективности терапии вследствие образования антител к БТ

Низкий риск развития иммуногенности при применении высоких доз КСЕОМИНА



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НЕВРОЛОГИЯ

Prospective analysis of neutralising antibody titres in secondary non-responders under continuous treatment with a botulinumtoxin type A preparation free of complexing proteins—a single cohort 4-year follow-up study

Harald Hefter,[1] Christian Hartmann,[1] Ulrike Kahlen,[1] Marek Moll,[1] Hans Bigalke[2]

To cite: Hefter H, Hartmann C, Kahlen U, *et al*. Prospective analysis of neutralising antibody titres in secondary non-responders under continuous treatment with a botulinumtoxin type A preparation free of complexing proteins—a single cohort 4-year follow-up study. *BMJ Open* 2012;**0**:e000646. doi:10.1136/bmjopen-2011-000646

► Prepublication history and additional material for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2011-000646).

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ABSTRACT

Objectives: In long-term botulinum neurotoxin treatment, loss of therapeutic efficacy may occur due to neutralising antibody formation. Preliminary results with incobotulinumtoxinA, a preparation free of complexing/accessory proteins, have indicated a low antigenicity. We hypothesised that continuous treatment with this botulinum neurotoxin preparation would not result in an increase in neutralising antibody titres (NABTs) in patients with pre-existing NABTs.

Design: Prospective, blinded cohort study.

Setting: Single centre in Germany.

Participants: Thirty-seven cervical dystonia patients with NABTs and partial secondary non-responsiveness to their previous botulinum neurotoxin type A treatment.

Intervention: Three-monthly intramuscular injections of incobotulinumtoxinA with a constant dose of 200 MU per injection during the first year; thereafter up to 500 MU for the next 36 months.

Outcome measures: Primary outcome measure: number of patients in whom NABTs declined below the initial titre after 48 months of incobotulinumtoxinA treatment or in whom titres had become negative within the 48 months. Secondary outcome measure: steepness of changes in NABT. NABTs were determined by mouse hemidiaphragm assay. Findings were compared to long-term data from 24 cervical dystonia patients who had developed NABTs and in whom treatment had been discontinued.

Results: Following a transient increase in the first 24 months under incobotulinumtoxinA treatment in some patients, NABTs declined well below the initial titre in the majority of patients. Test assay results were negative in most of the patients followed for more than 36 months. NABTs seemed to decline into the negative detection range as rapidly under incobotulinumtoxinA treatment as after cessation of botulinum neurotoxin therapy.

Conclusions: The reduction of NABTs despite continuous treatment with incobotulinumtoxinA indicates low antigenicity of incobotulinumtoxinA. This might have implications on restrictions such as minimum injection intervals of ≥10 weeks currently in place for maintaining successful long-term application of botulinum neurotoxin.

ARTICLE SUMMARY

Article focus
- Evaluation of antigenicity of incobotulinumtoxinA, a botulinum neurotoxin type A preparation free of complexing proteins for the treatment of cervical dystonia.

Key messages
- Secondary non-responders to conventional type A preparations showed a decline in neutralising antibody titres despite continuous treatment with incobotulinumtoxinA over a period of up to 50 months.
- Neutralising antibody titres seemed to decline into the negative detection range as rapidly under incobotulinumtoxinA treatment as after cessation of botulinumtoxin therapy.
- These results indicate low antigenicity of incobotulinumtoxinA.

Strengths and limitations of this study
- Till date, this study is the largest investigation of secondary non-responders with neutralising antibodies against botulinumtoxinA.
- The continuous treatment with incobotulinumtoxinA in secondary non-responders according to current knowledge of immunogenicity of botulinumtoxins should have resulted in boostering of antibody titres. Instead an unexpected decline of antibody titres was observed.
- This is an interesting finding despite the small sample size (n=37). Monocentric data have to be confirmed in multicentre studies.

Проспективный анализ титров нейтрализующих антител у пациентов с вторичной рефрактерностью, получающих длительную терапию ботулиническим токсином типа А, свободным от комплексообразующих белков — 4-летнее исследование

Hefter H, Hartmann C, Kahlen U, et al

НЕВРОЛОГИЯ

Дизайн исследования

Цель: Выявить снижение титра нейтрализующих антител (НА) в крови у пациентов после применения Inco-BTA, свободного от комплексообразующих белков[1]

Пациенты с цервикальной дистонией.

- *с высоким уровнем НА*
- *частичной вторичной нечувствительностью к БТА*
- **N=37**

Инкоботулотоксин А

Inco-BTA вводили каждые 3 месяца в дозе 200 МЕ в течение 1 года

Inco-BTA вводили в дозе 500 МЕ в течение 3-х лет

Результаты применения КСЕОМИНа показали его низкую степень иммуногенности:

При применении Ксеомина у пациентов с уже развившейся нечувствительностью к БТА на фоне применения токсина с комплексообразующими белками:

- значительно снижается уровень антител
- восстанавливается клинический ответ после перевода пациента на Ксеомин.

[1] Hefter H, Hartmann C, Kahlen U, et al. BMJ Open 2012;0:e000646. doi:10.1136/bmjopen-2011-0006462. Greensboro, NC: Merz Pharmaceuticals; 2010. Xeomin®:

Ксеомин® действует быстрее, чем Ботокс® и Диспорт® при коррекции морщин глабеллы

Clinical, Cosmetic and Investigational Dermatology

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ORIGINAL RESEARCH

Onset and duration of effect of incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA in the treatment of glabellar frown lines: a randomized, double-blind study

This article was published in the following Dove Press journal:
Clinical, Cosmetic and Investigational Dermatology
23 September 2013
Number of times this article has been viewed

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Daryousch Parvizi[1]
Herwig Friedl[2]
Maria Wiedner[1]
Simone May[1]
Bettina Kranzelbinder[3]
Paul Wurzer[1]
Bengt Hellbom[1,†]

[1]Department of Plastic and Reconstructive Surgery, Medical University Graz, Graz, Austria; [2]Institute of Statistics, Graz University of Technology, Graz, Austria; [3]Department of Dermatology, Medical University Graz, Graz, Austria

[†]Professor Bengt Hellbom passed away in September 2012

Background: Three botulinum neurotoxin type A preparations (incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA) are widely approved in Europe and in the US for the treatment of glabellar frown lines. The purpose of this study was to determine and compare the time to onset and duration of treatment effect of incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA for the treatment of glabellar frown lines.

Subjects and methods: Subjects aged 20–60 years with moderate to severe glabellar frown lines received one treatment of either 21 units (U) incobotulinumtoxinA, 21 U onabotulinumtoxinA, or 63 U abobotulinumtoxinA. Assessments were made over a period of 180 days. Onset of treatment effect was defined as the day that the observer noted a decrease in glabellar muscle activity compared with baseline photographs and videos. Duration of treatment effect was defined as the time until glabellar muscle action returned to the baseline level. Analyses were performed using a Weibull log(T) regression model.

Results: The study enrolled 180 subjects; 60 per group. For all three products, onset of treatment effect occurred earlier in female subjects compared to male subjects. For both sexes, a significantly earlier time to onset of treatment effect was seen for incobotulinumtoxinA compared to onabotulinumtoxinA and abobotulinumtoxinA; in female subjects these times were 3.02 days, 5.29 days, and 5.32 days, respectively. The duration of treatment effect was longer for incobotulinumtoxinA compared to onabotulinumtoxinA and abobotulinumtoxinA; for all products, treatment effect duration was longer in females than in males. Time to onset was not a predictor of treatment duration.

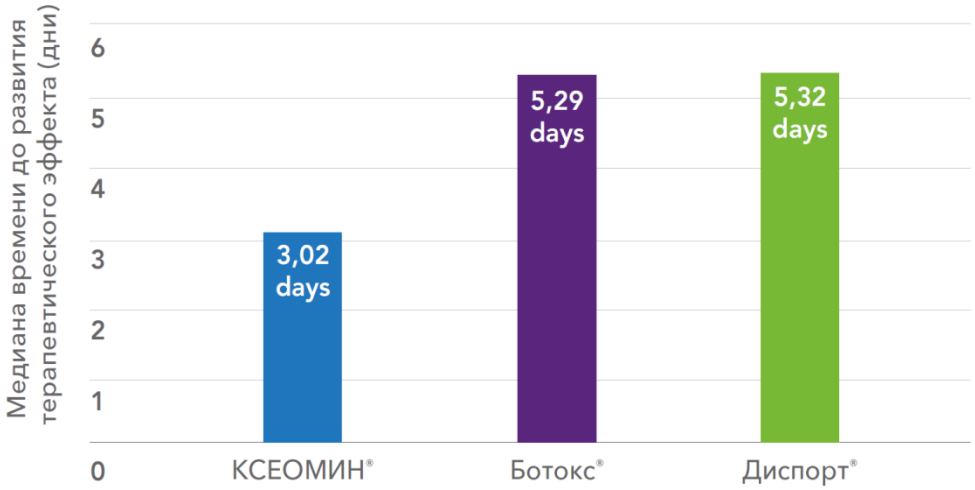
Conclusion: IncobotulinumtoxinA demonstrated a more rapid onset and a longer duration of treatment effect than onabotulinumtoxinA (1:1 dose ratio) and abobotulinumtoxinA (1:3 dose ratio). Onset of effect was faster and duration of effect was longer in female subjects compared to male subjects.

Keywords: botulinum neurotoxin type A, glabellar frown lines, incobotulinumtoxinA, regression analysis

Время наступления и длительность эффекта инкоботулотоксина А, онаботулотоксина А и абоботулотоксина А при коррекции глабеллы: рандомизированное, двойное-слепое исследование

Ксеомин® действует быстрее, чем Ботокс® и Диспорт® при коррекции морщин глабеллы

Время до начала развития эффекта после применения препаратов КСЕОМИН, Диспорт, Ботокс



Пациенты с выраженностью морщин глабеллы по шкале 2-3 балла MERZ

- **N=180**
- **21 ЕД КСЕОМИН**
- **21 ЕД БОТОКС**
- **или 63 ЕД ДИСПОРТ**

Средняя **длительность эффекта** после применения препаратов КСЕОМИН, Диспорт, Ботокс, дни

	IncobotulinumtoxinA	OnabotulinumtoxinA	Abobotulinumtoxin A
Женщины	**146.12**	**140.65**	**139.69**
Мужчины	**121.14**	**116.61**	**115.81**

Rappl et al., Clinical, Cosmetic and Investigational Dermatology 2013:6 1-9

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A Prospective, Neurophysiologic Comparative Study to Assess the Efficacy and Duration of Effect of IncobotulinumtoxinA and AbobotulinumtoxinA in the Treatment of Crow's Feet

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ABSTRACT

This randomized, rater-blind, split-face study compared the safety and efficacy of incobotulinumtoxinA and abobotulinumtoxinA for the treatment of crow's feet. Nine units of incobotulinumtoxinA were administered to the lateral periorbital region of one side of the face and 27 units of abobotulinumtoxinA to the other in healthy subjects (aged 35–55 years) with moderate-to-severe crow's feet at rest (2–3 points on the 5-point Merz Aesthetics Scale [MAS]). Investigators assessed efficacy using the MAS, while subjects assessed using a 9-point global assessment scale. Secondary objectives included electromyography to assess muscle activity before injection and at 2 weeks, 4 months, and 6 months afterwards. Twenty women were enrolled and 18 completed the study. At rest and maximum smile, at each time point, the mean wrinkle scores were significantly lower ($P \leq 0.05$) than baseline for both treatments. No differences were noted between treatments. Responder (≥ 1-point improvement from baseline) rates for both products were 100% and 83% at 2 weeks and 4 months post-treatment, respectively. At 6 months post-treatment, responder rates were 67% and 61% for incobotulinumtoxinA and abobotulinumtoxinA, respectively. For both, the maximum changes in electromyography parameters were observed 2 weeks post-treatment. A response was maintained for 6 months ($P \leq 0.05$ vs baseline). Both treatments were well tolerated; only mild adverse events were reported. In conclusion, for treatment of crow's feet, incobotulinumtoxinA and abobotulinumtoxinA (1:3 dose) demonstrated comparable efficacy in terms of magnitude and longevity of effect. Both products demonstrated a high responder rate, with the response being maintained for 6 months in the majority.

J Drugs Dermatol. 2015;14(11):1291-1296.

INTRODUCTION

Botulinum toxin type A (BoNT/A) formulations are used in aesthetics for the treatment of wrinkles of the upper

In 2009, the US Food and Drug Administration introduced product labelling to note that potency units (U) are specific

Сравнительное слепое split-face исследование эффективности abobotulinumtoxinA (Диспорт) и incobotulinumtoxinA (Ксеомин) в эквивалентности 3:1 для лечения латеральных периорбитальных морщин.

Цель: Сравнить эффективность и безопасность Inco-BTA и Abo-BTA в соотношении доз 1:3 в лечении латеральных периорбитальных морщин («гусиные лапки»)

Пациенты

- с мимическими морщинами в верхней части лица
- FWS - 2-3степень
- N=20
- Длительность – 6 месяцев

Инкоботулинумтоксин А

Доза - 9 ЕД с одной стороны лица (справа)

Абоботулинумтоксин А

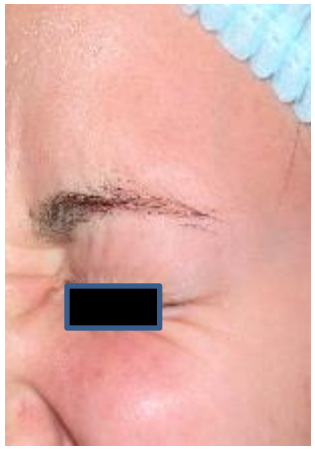
Доза - 27 ЕД с другой стороны лица (слева)

Данные электромиографии (в ответ на стимуляцию лицевого нерва) до инъекций, на 14 день, 4-й и 6-й месяцы после инъекций

Клинический ответ и безопасность на 14 день, 4-й и 6-й месяцы после инъекций

Saybel A, Artemenko A, Nikitin S, et al. A prospective, neurophysiologic comparative study to assess the efficacy and duration of effect of incobotulinumtoxinA and abobotulinumtoxinA in the treatment of crow's feet. *J Drugs Dermatol*. 2015;14(11):1291–6.

Фото пациентов при максимальном напряжении до, через 2 недели, через 4 и 6 месяцев

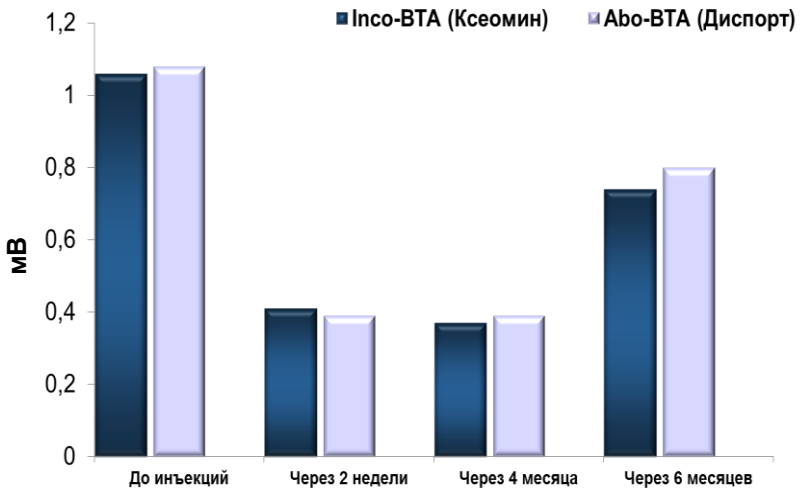
	до процедуры	через 14 дней	через 4 мес	через 6 мес
Диспорт				
Ксеомин				

Saybel A, Artemenko A, Nikitin S, et al. A prospective, neurophysiologic comparative study to assess the efficacy and duration of effect of incobotulinumtoxinA and abobotulinumtoxinA in the treatment of crow's feet. *J Drugs Dermatol*. 2015;14(11):1291–6.

Для внутреннего пользования

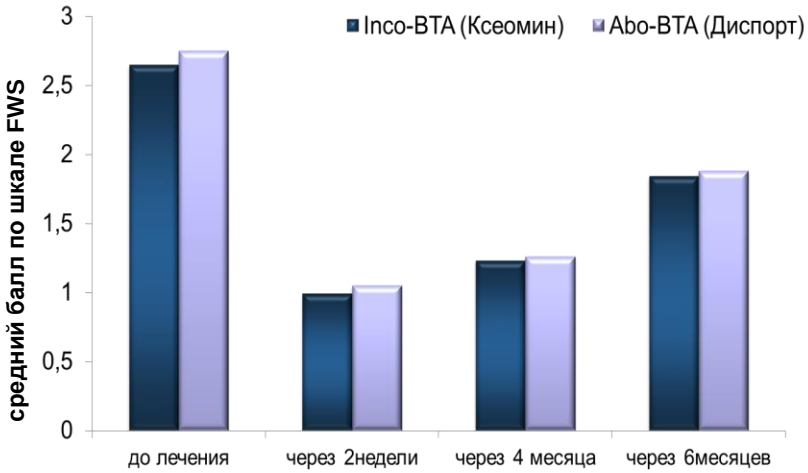
Ксеомин® и Диспорт® были одинаково эффективными и безопасными в лечении морщин глаза

Амплитуда М-ответа: динамика после инъекций препаратов БТА



Регистрация показателей М-ответа осуществлялась с круговой мышцы глаза

Средний балл по шкале FWS при максимальном сокращении, оцененный пациентом



Безопасность

Не было отмечено разницы в переносимости препаратов

16 пациентов отметили переносимость как «очень хорошую», 2 пациента отметили, как «хорошую» переносимость для обоих препаратов

Отек на месте инъекции (2 случая)

Не было зафиксировано серьезных побочных эффектов

Процент ответивших на терапию			
	2 недели (n=20)	**4 месяца (n=18)**	**6 месяцев (n=18)**
КСЕОМИН	100%	83%	**67%**
ДИСПОРТ	100%	83%	**61%**

Saybel A, Artemenko A, Nikitin S, et al. A prospective, neurophysiologic comparative study to assess the efficacy and duration of effect of incobotulinumtoxinA and abobotulinumtoxinA in the treatment of crow's feet. *J Drugs Dermatol*. 2015;14(11):1291–6.

В ходе клинических исследований наблюдали минимальную частоту встречаемости отека и птоза в области глаз при применении Ксеомина

Repeated Botulinum Toxin A Injections for the Treatment of Lines in the Upper Face: A Retrospective Study of 4,103 Treatments in 945 Patients

Berthold Rzany, MD, ScM,* Dorothee Dill-Müller, MD,† Doris Grablowitz, MD,‡ Marc Heckmann, MD,§ and David Caird, PhD,¶ on behalf of the German–Austrian Retrospective Study Group

BACKGROUND Although botulinum toxin type A (BoNT-A) is a common aesthetic intervention, there are few published data on treatment over more than two cycles.

OBJECTIVE To evaluate the effectiveness/safety of repeated doses of BoNT-A (Dysport, Ipsen Ltd., Slough, UK) in the upper face for reduction of wrinkles.

METHODS Retrospective, cross-sectional patient chart review from 945 patients who had received a minimum of three consecutive, documented treatment cycles.

RESULTS The glabella was treated most frequently (93.9%), with the majority (81.5%) of patients receiving treatment in more than one area of the face. BoNT-A treatments were combined with other aesthetic procedures in 57.5% of cases, mostly with fillers (37.1%). There was no evidence of tachyphylaxia: the dose applied, the interval between treatments, and satisfaction with the results remained stable over the course of treatment. Adverse events were those expected with BoNT-A treatment (most common: local bruising and ptosis) and were all mild or moderate in intensity. There was no sign of any cumulative adverse effects: indeed, the adverse-event rate decreased in later treatment cycles.

CONCLUSIONS Long-term, repeated injections of BoNT-A for corrections of wrinkles in the upper face yield a continuously high level of safety and effectiveness in actual practice.

This study was funded by Ipsen. David Caird is an employee of Ipsen.

Review Article

OnabotulinumtoxinA for Treatment of Moderate to Severe Crow's Feet Lines: A Review

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Alastair Carruthers, MD, BM, BCh, FRCPC, FRCP (Lon); Suzanne Bruce, MD; Sue Ellen Cox, MD; Michael A.C. Kane, MD; Elisabeth Lee, MPH; and Conor J. Gallagher, PhD

Abstract

Lateral canthal lines or crow's feet lines (CFL) may be treated with onabotulinumtoxinA. We identified several key concepts important to understanding use of onabotulinumtoxinA for treatment of moderate-to-severe CFL. To contextualize and integrate data on the recommended dose and injection patte of onabotulinumtoxinA for treatment of CFL, we summarized data from pivotal clinical studies in the development of onabotulinumtoxinA for treatmen CFL. Data from key studies of onabotulinumtoxinA for CFL are presented. The efficacy and safety of onabotulinumtoxinA treatment of moderate-to-sev CFL were evaluated in 2 randomized, controlled phase 3 studies comprising 1362 patients. The 24U total dose of onabotulinumtoxinA used in th studies was based on a phase 2 dose-ranging trial. Two injection patterns were available to investigators; each involved 3 injection sites per side in lateral orbicularis oculi muscle. A cross-sectional analysis of photographs from the phase 3 trials provided detailed information on the frequency of 4 dist CFL patterns. In the primary efficacy analysis for each phase 3 trial, CFL responder rates were significantly greater with onabotulinumtoxinA vs placebo day 30 ($P < .001$). Eyelid edema (1%) was the only adverse event reported in ≥1% of patients receiving onabotulinumtoxinA, occurring more freque with onabotulinumtoxinA than with placebo. The studies showed that onabotulinumtoxinA is effective and generally well-tolerated for CFL treatme Additionally, 2 different injection patterns allow physicians to tailor treatment based on a patient's CFL pattern.

Accepted for publication January 18, 2016; online publish-ahead-of-print March 15, 2016.

The use of onabotulinumtoxinA (Botox Cosmetic; Allergan,

The efficacy and safety of onabotulinumtoxinA in C

A Randomized, Double-Blind Trial to Investigate the Equivalence of IncobotulinumtoxinA and OnabotulinumtoxinA for Glabellar Frown Lines

Michael A. C. Kane, MD,* Michael H. Gold, MD,† William P. Coleman, III, MD,‡ Derek H. Jones, MD,§ Emil A. Tanghetti, MD,‖ Tina S. Alster, MD,¶ Tom E. Rohrer, MD,# Cheryl M. Burgess, MD,** Ava T. Shamban, MD,†† and Eleanor Finn, PhD‡‡

BACKGROUND IncobotulinumtoxinA and onabotulinumtoxinA are indicated for the temporary improvement in the appearance of glabellar frown lines (GFL). This is the first randomized direct comparative study to date, at the Food and Dru

OBJECTIVE To (20 U) for the trea

MATERIALS AND (18–50 years), en a 4-month observ

RESULTS At th alent to onabotu margin of equiv treatment as ass satisfaction ratin well tolerated.

CONCLUSION E onabotulinumtox es were obs

tudy was sp tigators for des service ica, Inc.

ORIGINAL A

Long-Tern Glabellar

Berthold Rzany, MD ScM, Timothy Corcoran Flynn, MD, Andrea Schlebe, MD, Moritz Heinz,‡ and Laura Harrington, PhD¶

BACKGROUND IncobotulinumtoxinA has been approved for treatment of glabellar frown lines (GFL) in the United States, all major European markets, South Korea, and Argentina and in Russia and Mexico for the treatment of mimic wrinkles and hyperkinetic facial lines, respectively.

OBJECTIVES Prospective, 2-year, open-label, multicenter, repeat-dose, Phase III trial investigating the safety and efficacy of incobotulinumtoxinA for the treatment of GFL.

METHODS Subjects with moderate or severe GFL on the Facial Wrinkle Scale (FWS), enrolled from previous trials, were treated with 20 U of incobotulinumtoxinA per cycle (up to eight treatment cycles, treatment interval at least 85 days). Efficacy was measured according to the investigator-assessed percentage of responders on the FWS (subjects with a score of 0 or 1) at rest and maximum frown on Day 30 of each cycle, subject assessments, and onset and duration of treatment effect.

RESULTS In 796 subjects, 77% to 88% were responders at rest, and 79% to 90% were responders at maximum frown. Onset was rapid; subjects reported effects in the first few days after treatment. No new tolerability or safety concerns were reported.

CONCLUSIONS IncobotulinumtoxinA injections were well tolerated and resulted in efficacy in the treatment of GFL for up to 2 years.

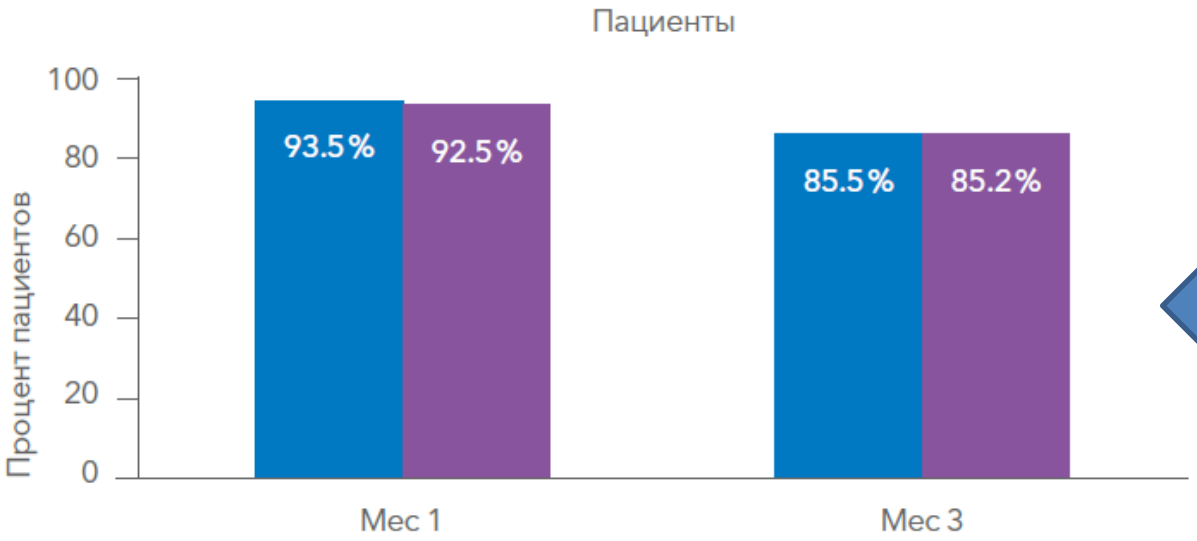
The authors have indicated significant interest with commercial supporters.

- **Число случаев птоза и отека в области век в группе Ксеомин 0,4 %[1]**
- **Встречаемость отеков и птоза у Ксеомина в исследовании 0,3%, что подтверждается исследованиями проведенными ранее[2]**
- **При применении Ксеомина частота птоза и отека в области век составляла 0% и 0,8% соответственно[3]**

1. Sattler G et al., Noninferiority of incobotulinumtoxinA, free from complexing proteins, compared with another botulinum toxin type A in the treatment of glabellar frown lines. Dermatol Surg 2010;36:2146–54.
2. Rzany B et al., Long-Term Results for IncobotulinumtoxinA in the Treatment of Glabellar Frown. Dermatol Surg 2013;39:95–103
3. Kane M. et al., A Randomized, Double-Blind Trial to Investigate the Equivalence of IncobotulinumtoxinA and OnabotulinumtoxinA for Glabellar Frown Lines. Dermatol Surg 2015;41:1310–1319

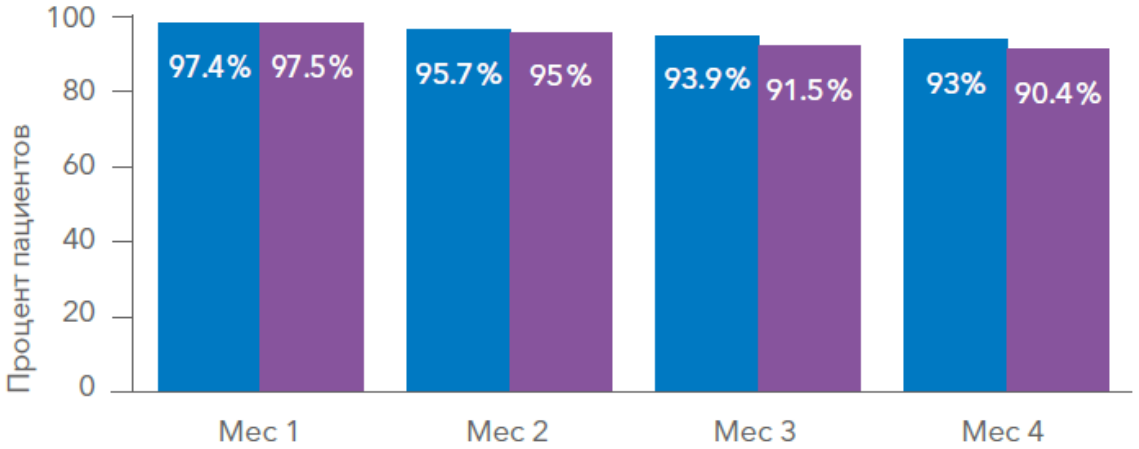
Высокий уровень удовлетворенности пациентов при применении КСЕОМИНА

КСЕОМИН 20 ЕД
БОТОКС 20 ЕД



Сравнительное Европейское исследование

КСЕОМИН 24 ЕД
БОТОКС 24 ЕД



Сравнительное Американское исследование

1. Одинаково высокая удовлетворенность пациентов, получавших КСЕОМИН или БОТОКС, при оценке в 1, 2, 3 и 4-й месяцы наблюдения.

2. % пациентов «слегка удовлетворены», «удовлетворены», «в высшей степени удовлетворены»

1. Sattler G, et al. Noninferiority of incobotulinumtoxinA, free from complexing proteins, compared with another botulinum toxin type A in the treatment of glabellar frown lines. Dermatol Surg. 2010;36 (Suppl 4):2146–2154

2. Kane M. et al., A Randomized, Double-Blind Trial to Investigate the Equivalence of IncobotulinumtoxinA and OnabotulinumtoxinA for Glabellar Frown Lines

Основательная доказательная база: у Ксеомина более 100 публикаций основанных на более чем 76 масштабных клинических исследованиях (2005-2016 гг)

	Общее количество исследований	Эффективность	Безопасность
Сравнительные Ботокс/Диспорт	19/8		
Несравнительные	49		
Эффективность			
Нижняя треть лица		23	
Высокая удовлетворенность		76	
Риски развития иммуногенности		11	
Быстрое наступление эффекта		4	
Безопасность			
Применение для Full-face			12
Нижняя треть лица			23