SYMPOSIUM
ANTEROS PROJECT

Biological treatments: the Genoa experience

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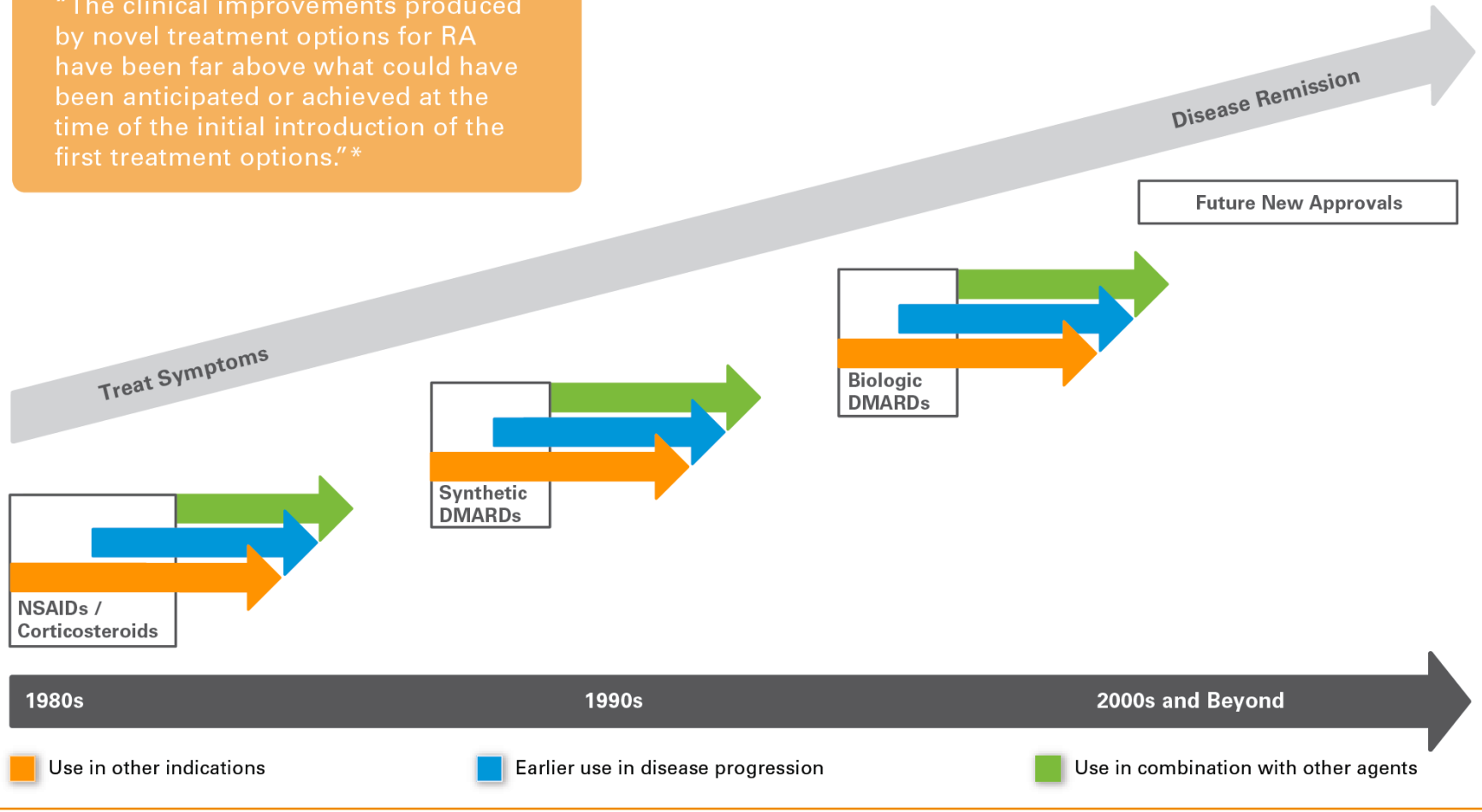
DISCLOSURES

Gerolamo Bianchi has received honoraria and/or consulting fees from Abbvie, Abiogen, Alfa-Wassermann, Amgen, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Jansenn, Medac, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Schering Plough, Servier and SPA.

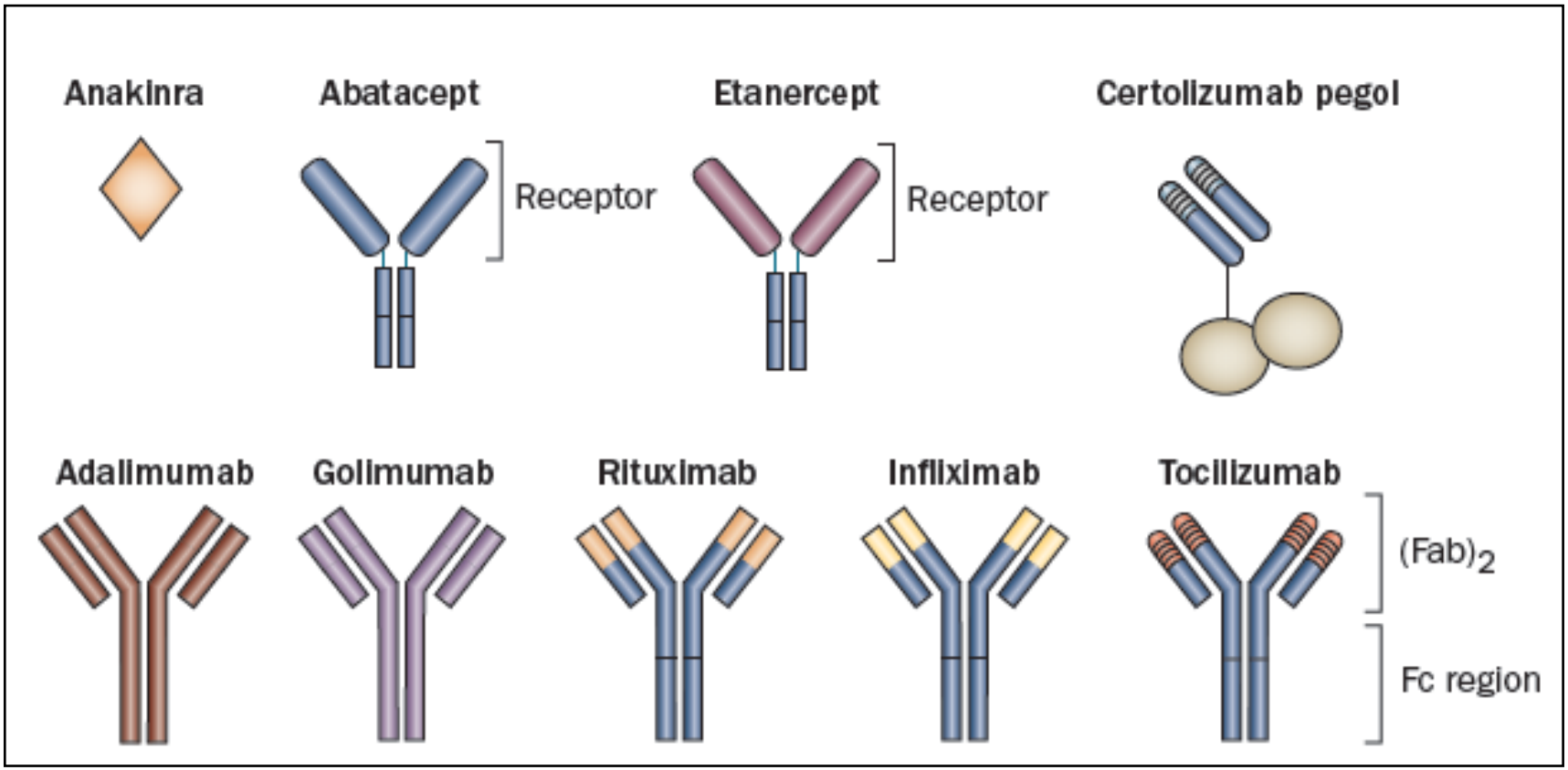
Rheumatoid Arthritis: The Evolution of Clinical Value for Patients

"The clinical improvements produced by novel treatment options for RA have been far above what could have been anticipated or achieved at the time of the initial introduction of the first treatment options."*



White Paper, Boston Healthcare, March 2013

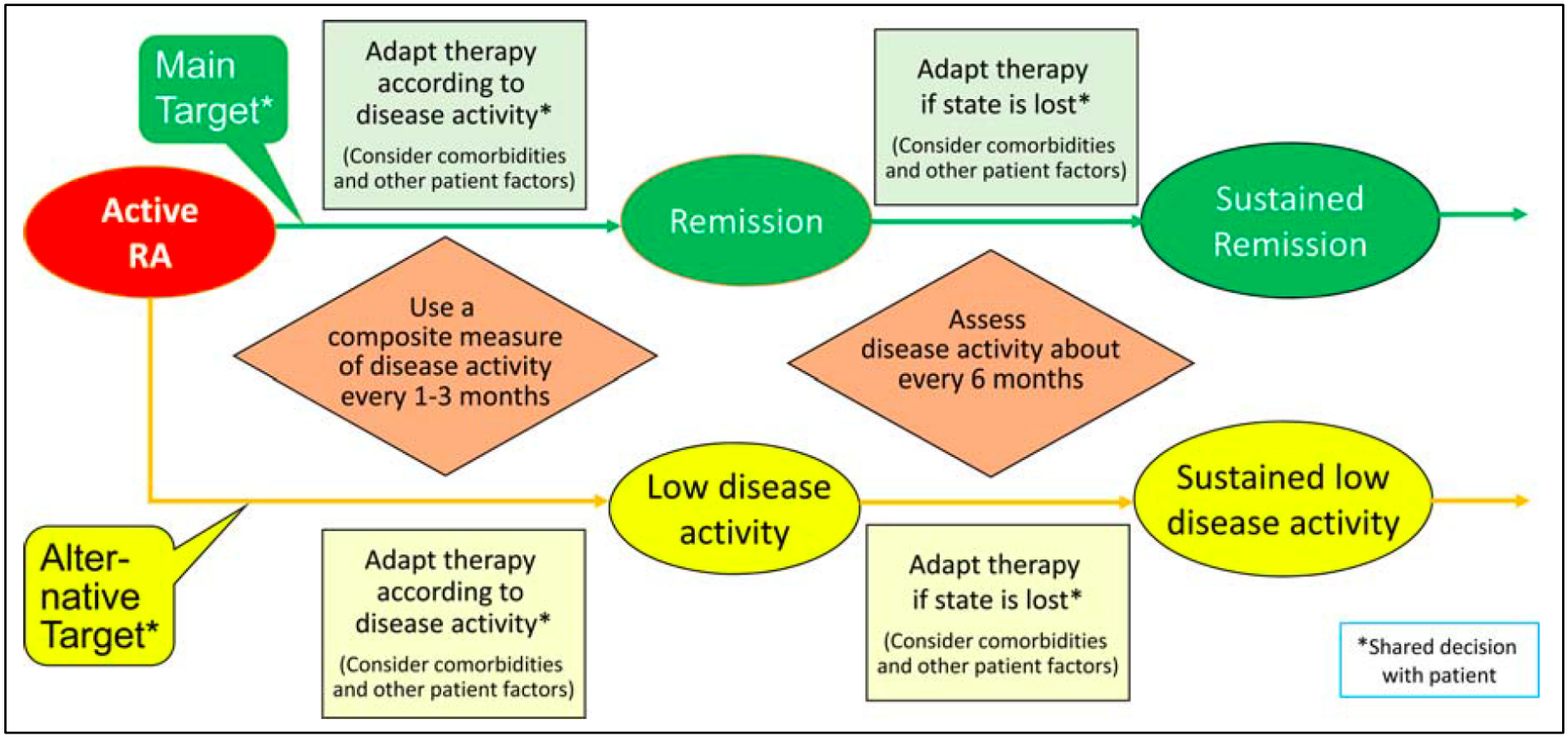
Biologic agents approved for the treatment of RA



van Vollenhoven R. Nat Rev Rheumatol 2011

EXTENDED REPORT

Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force



Smolen JS, et al. Ann Rheum Dis 2015

Valutazione Attività di Malattia

DAS	> 3.7	< 3.7		< 2.4	< 1.6	(*)
DAS 28	> 5.1	< 5.1		< 3.2	< 2.6	(*)
SDAI	> 26	< 26		< 11	< 3.3	(**)
CDAI	> 22	< 22		< 10	< 2.8	(**)

(*) van Gestel AM et al. *Arthrtis Rheum 1998; 41: 1845-50*
(**) D.Aletaha, J.Smolen *Clin Exp Rheumatol 2005; 23 (Suppl.39): S100-S108*

ACR/EULAR 2011 Provisional Definitions of Remission for Clinical Trials

- **Boolean Based Definition**
  At any time point, a patient must satisfy all of the following:
  - Tender Joint Count ≤1
  - Swollen Joint Count ≤1
  - CRP ≤1 mg/dL
  - Patient Global Assessment ≤1 (on a 0-10 scale)
- **Index Based Definition**
  At any time point, a patient must have SDAI ≤3.3

Review

Cost-effectiveness of biologic treatment for rheumatoid arthritis in clinical practice: An achievable target?

Vittorio Modena [a,*], Gerolamo Bianchi [b], Dario Roccatello [a]

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A B S T R A C T

The burden of illness of rheumatoid arthritis (RA) falls on patients, families and society through the direct costs, indirect costs, and intangible costs. A large number of RA cost-of-illness studies have been performed in recent decades with discrepant results due to patient heterogeneity, and different health-care organization, employment rate or social support, job opportunities, and methodologies used to calculate the costs. The greatest burden of RA is the indirect and the intangible costs, but how to estimate them remains controversial. The systematic use of traditional disease modifying anti rheumatic drugs has changed the evolution of the disease. However, a considerable improvement in the management of RA has been obtained since the advent of biologic response modifiers. The use of these drugs, which have demonstrated greater efficacy than conventional therapies, have tripled the direct costs of RA, which rose from about € 4000 to roughly € 12,000, in a period of five years, from 2000 to 2005. The present paper is aimed to examine the effects of this change in therapeutic strategy.

Modena V et al. Autoimmun Rev 2013

Review

Cost-effectiveness of biologic treatment for rheumatoid arthritis in clinical practice: An achievable target?

- Until the cost of biological drugs drops, the challenge is to optimise their use.

- This can be done through:
  - the early treatment of patients who do not respond to traditional DMARDs
  - by identifying the group of patients in whom biologics can be successfully discontinued after a reasonable time without subsequent relapse of disease
  - by identifying the subjects whose disease activity can be kept low by administering traditional DMARDs alone after the biologics.

Modena V et al. Autoimmun Rev 2013

Italian National Health System

- National Fund assigned by Central Government but managed by Regional Government
- Local Health administrations
- Budget allocation to Departments
- Tight cost minimization policy
- Drug budget respect required
- Budget monitored every 6 months (tight control)

Department of Locomotor System
Division of Rheumatology
ASL3-Genovese

Optimization protocol for the use of biological treatments

Year 2014 - 2015

ASL3 Genovese – Dipartimento Specialita' Mediche – U.O. Reumatologia

LINEE GUIDA PER LA RIDUZIONE DI DOSAGGIO DEI FARMACI BIOLOGICI
Artrite Reumatoide e Artrite Psoriasica.

Se a 1 controllo a distanza di 3 mesi DAS28: < 2.6 provare a ridurre:

- ENBREL 50 mg ogni 10 gg
- HUMIRA 40 mg ogni 3 settimane
- CIMZIA 200 mg ogni 3 settimane
- SIMPONI 50 mg ogni 5 settimane
- REMICADE ogni 9 settimane
- ORENCIA ogni 5 settimane
- RO-ACTEMRA ogni 5 settimane
- MABTHERA ogni 7 mesi

Se dopo 3 mesi non c'è stata riacutizzazione, provare a ridurre:

- ENBREL 50 mg ogni 2 settimane
- HUMIRA 40 mg ogni 4 settimane
- CIMZIA 200 mg ogni 4 settimane
- SIMPONI 50 mg ogni 6 settimane
- REMICADE ogni 10 settimane
- ORENCIA ogni 6 settimane
- RO-ACTEMRA ogni 6 settimane
- MABTHERA ogni 8 mesi

Se dopo 3 mesi il paziente è in remissione: TJC ≤ 1, SJC ≤ 1, PCR ≤ 1 mg\dl, PGA ≤ 10 mm,o SDAI ≤ 3.3
Sospende la terapia con biologici e continua con DMARDs a dosaggio pieno.
In caso di peggioramento clinico, aumentare il dosaggio del DMARDs fino al massimo consentito e\o tollerato. Se tale aggiustamento terapeutico non è sufficiente, il paziente sarà nuovamente inserito in terapia con biologici.

LINEE GUIDA PER LA RIDUZIONE DI DOSAGGIO DEI FARMACI BIOLOGICI
Spondilite Anchilosante.

Se a un controllo a distanza di 3 mesi il BASDAI < 50% rispetto al valore iniziale, VAS dolore <10, VES e PCR negativi, provare a ridurre:

- ENBREL 50 mg ogni 10 gg
- HUMIRA 40 mg ogni 3 settimane
- SIMPONI 50 mg ogni 5 settimane
- REMICADE ogni 9 settimane

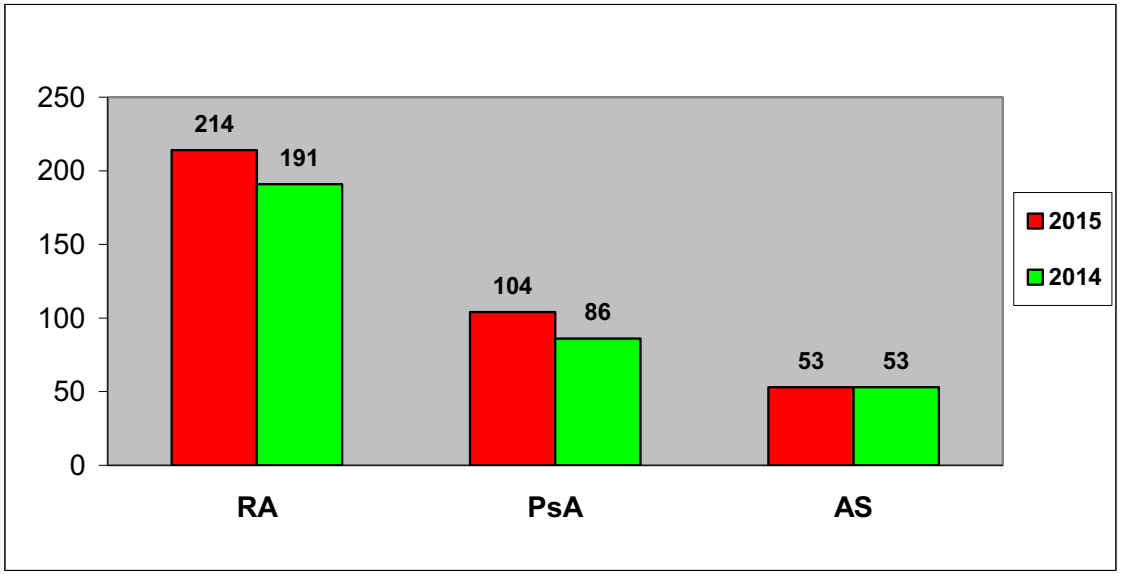
Se dopo 3 mesi non c'è stata riacutizzazione, provare a ridurre:

- ENBREL 50 mg ogni 2 settimane
- HUMIRA 40 mg ogni 4 settimane
- SIMPONI 50 mg ogni 6 settimane
- REMICADE ogni 10 settimane

Se dopo 3 mesi il paziente è in remissione: BASDAI < 50% rispetto al valore iniziale, VAS dolore <10, VES e PCR negativi. Sospende la terapia con biologici.

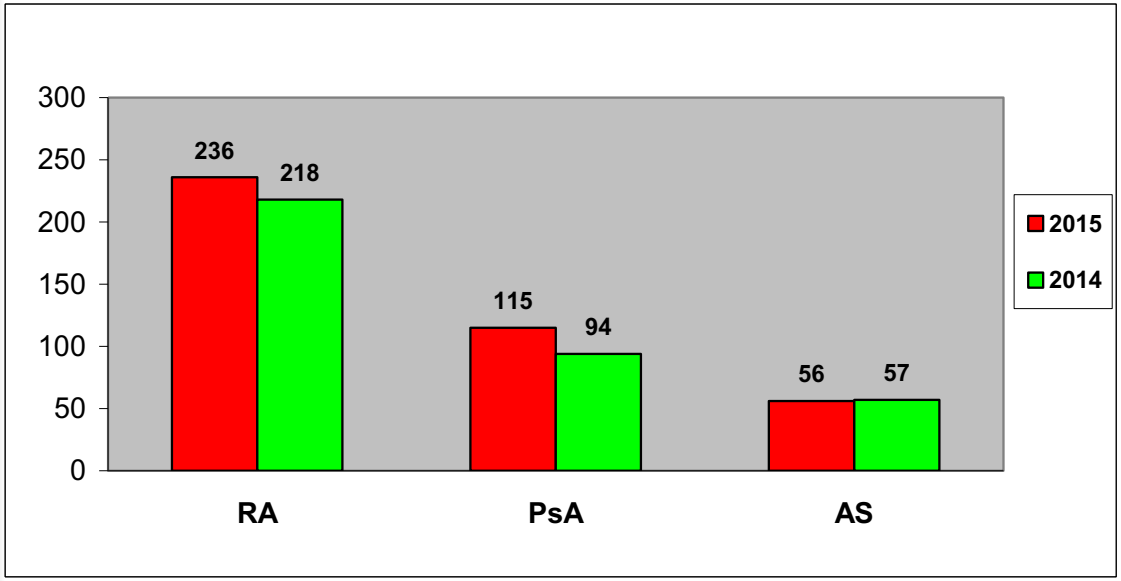
In caso di peggioramento clinico, il paziente sarà nuovamente inserito in terapia con biologici.

Pazienti e linee di terapia per patologia



2015:
371 pazienti

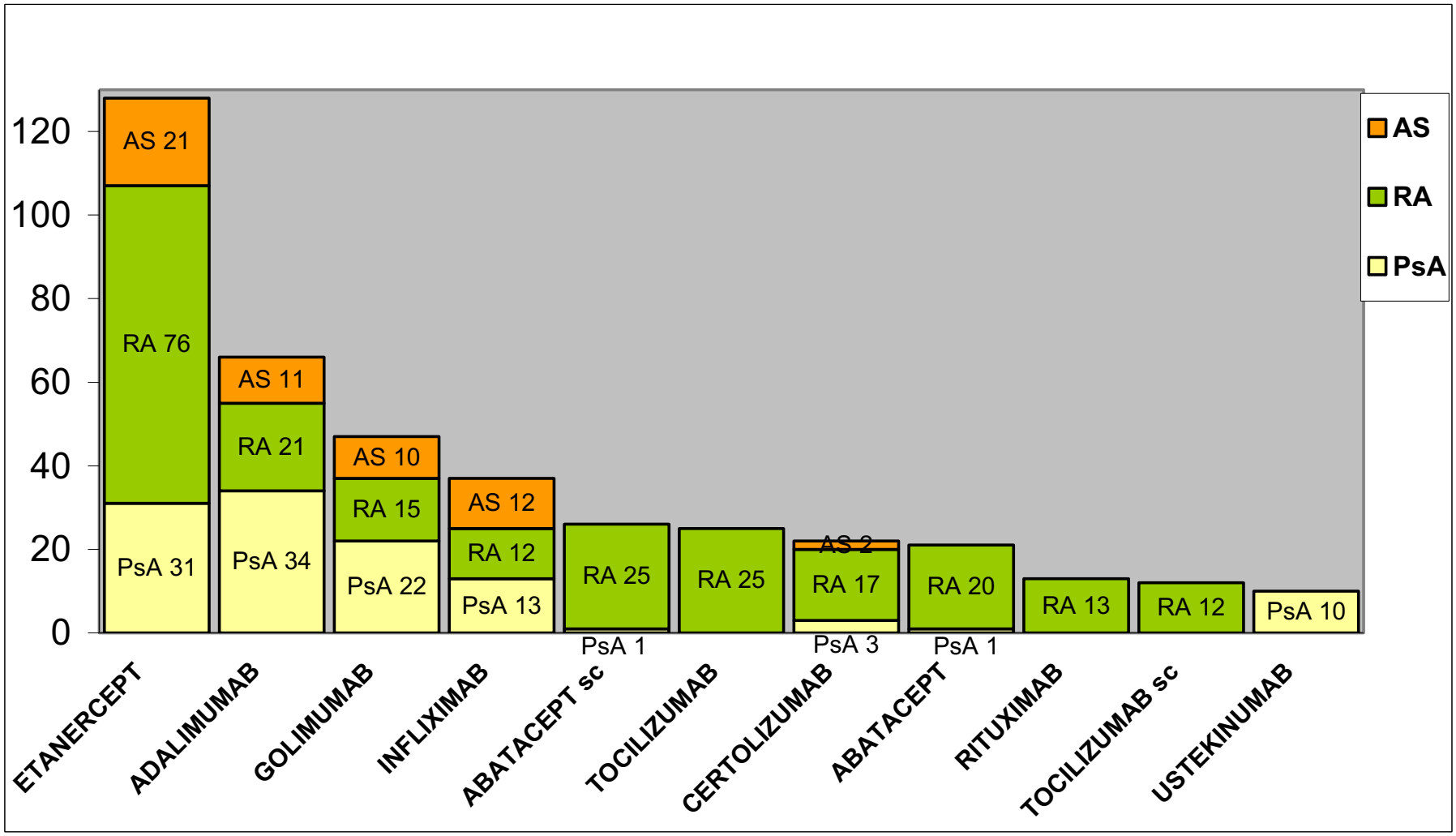
2014:
330 pazienti



2015:
407 linee di terapia

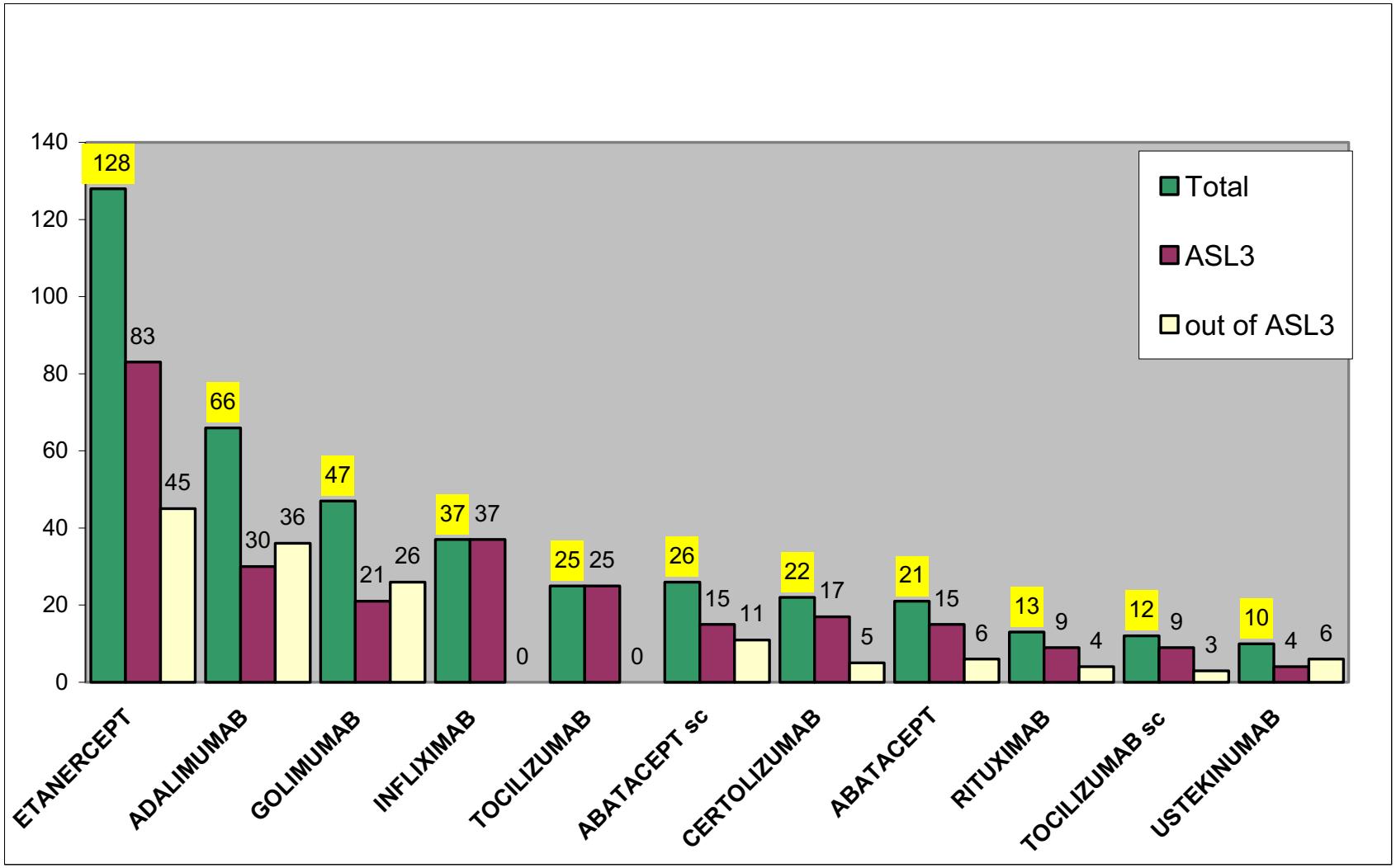
2014:
369 linee di terapia

Linee di terapia per farmaco e patologia - 2015



Numero 407

Linee di terapie per farmaco e provenienza - 2015



Numero 407 (ASL3 265 [65.1%] – NON ASL3 142 [34.9%])

OPTIMIZATION PROTOCOL
Economic analysis

- **Standard cost**

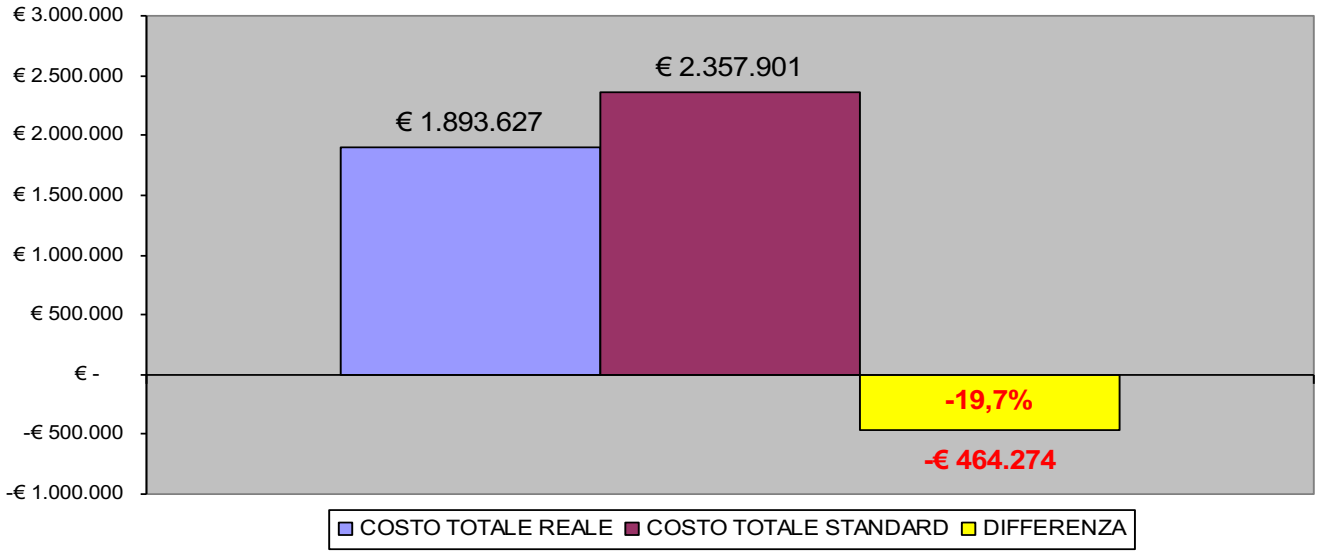
  Drug price according RCPs, multiplied by 52 weeks of treatment.

- **Real cost**

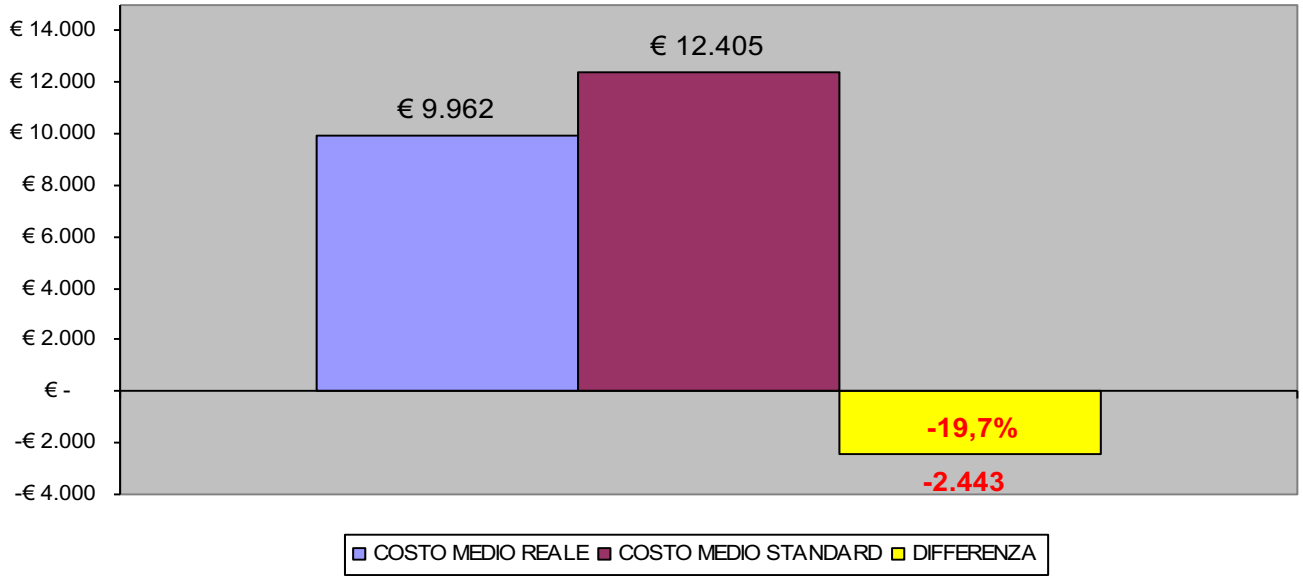
  Effective amount of money spent for each drug on annual basis, inclusive of discount policies.

Analysis limited to ASL3 patients because of accuracy of data

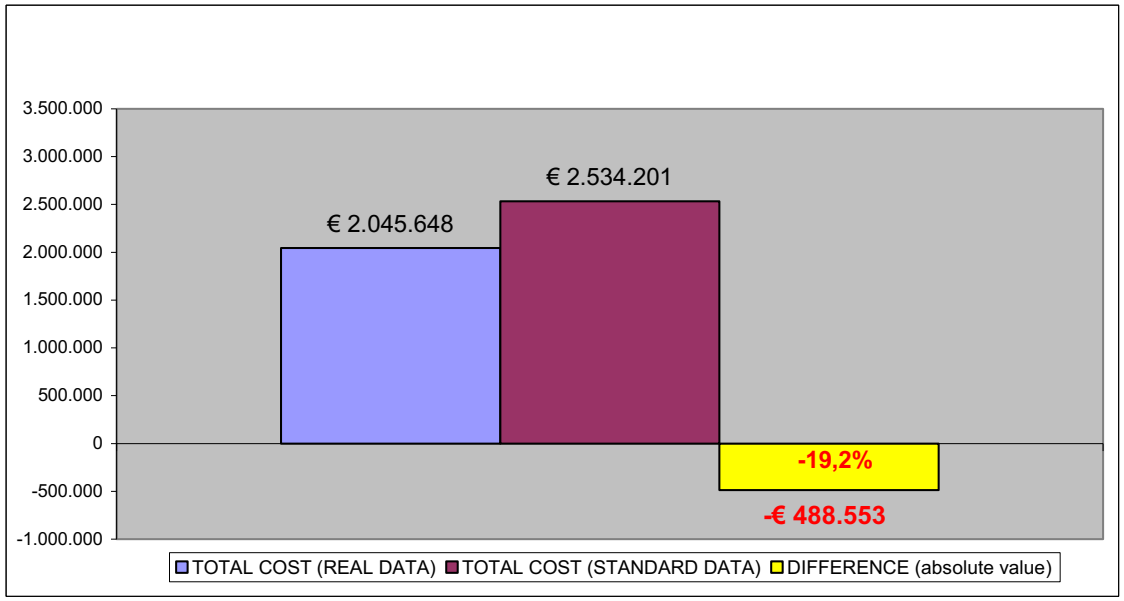
ASL3 – Costo totale (**reale e standard**) e differenza - 2014



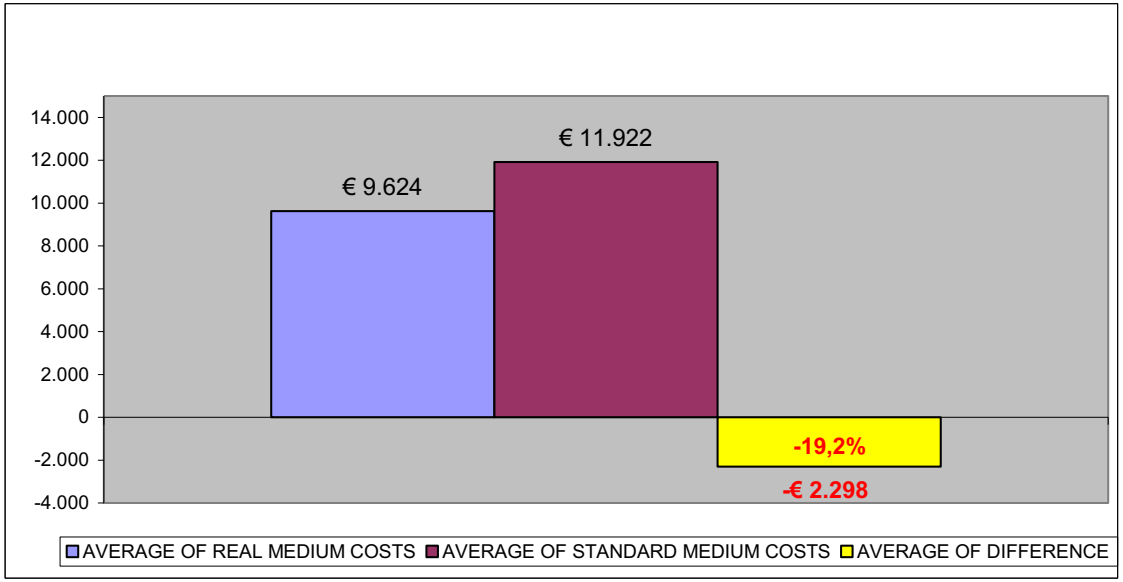
ASL3 – Costo medio farmaco (**reale e standard**) e differenza - 2014

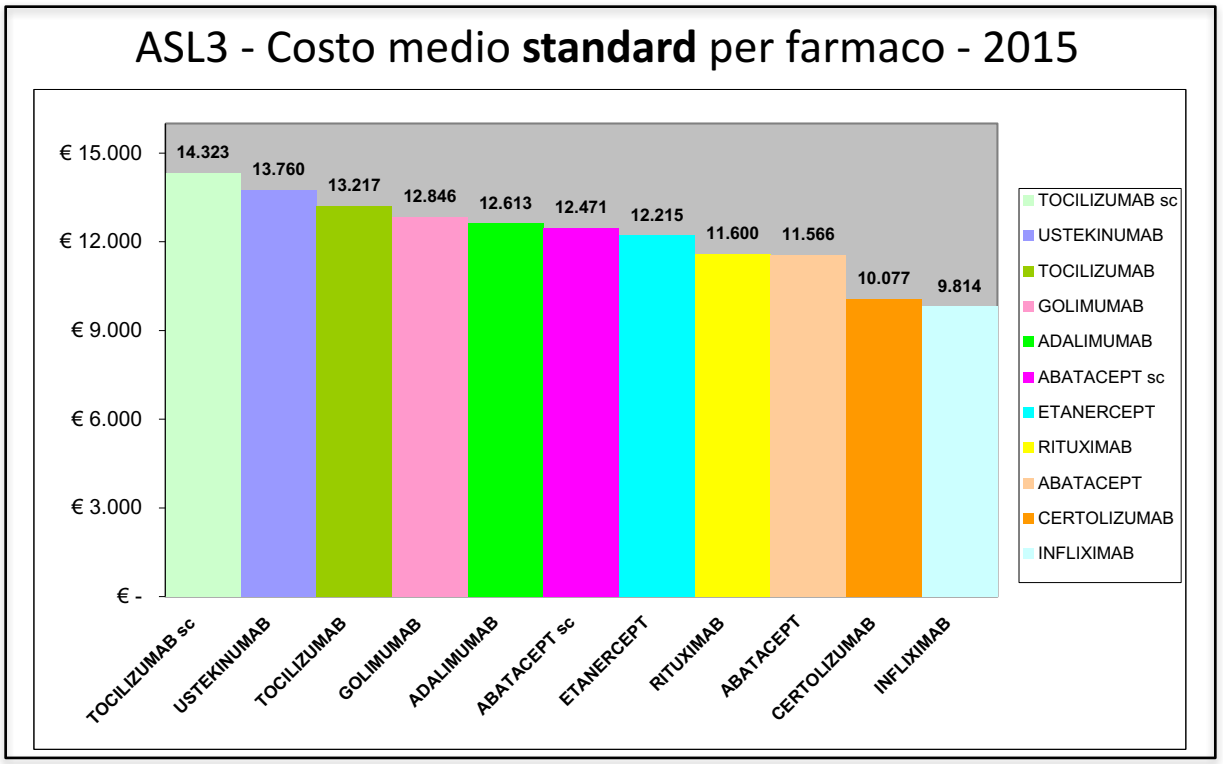


ASL3 – Costo totale (**reale e standard**) e differenza - 2015



ASL3 – Costo medio farmaco (**reale e standard**) e differenza - 2015




ASL3 - Costo medio **standard** per farmaco - 2015
€ 15.000
€ 12.000
€ 9.000
€ 6.000
€ 3.000
€ -
14.323
13.760
13.217
12.846
12.613
12.471
12.215
11.600
11.566
10.077
9.814
TOCILIZUMAB sc
USTEKINUMAB
TOCILIZUMAB
GOLIMUMAB
ADALIMUMAB
ABATACEPT sc
ETANERCEPT
RITUXIMAB
ABATACEPT
CERTOLIZUMAB
INFLIXIMAB
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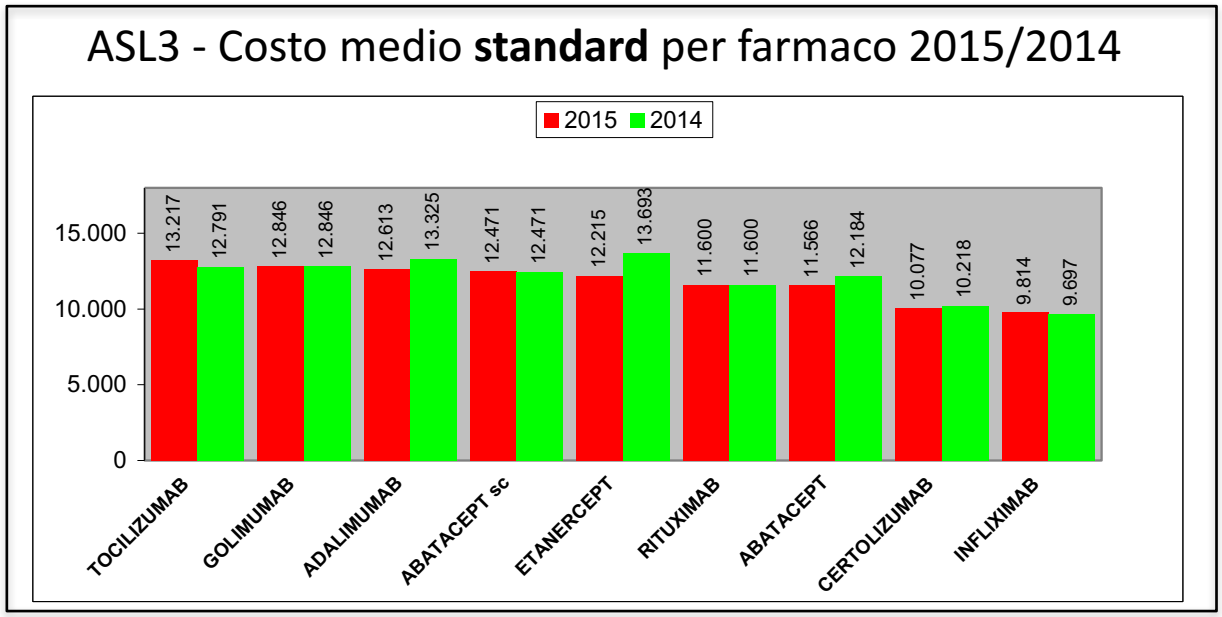
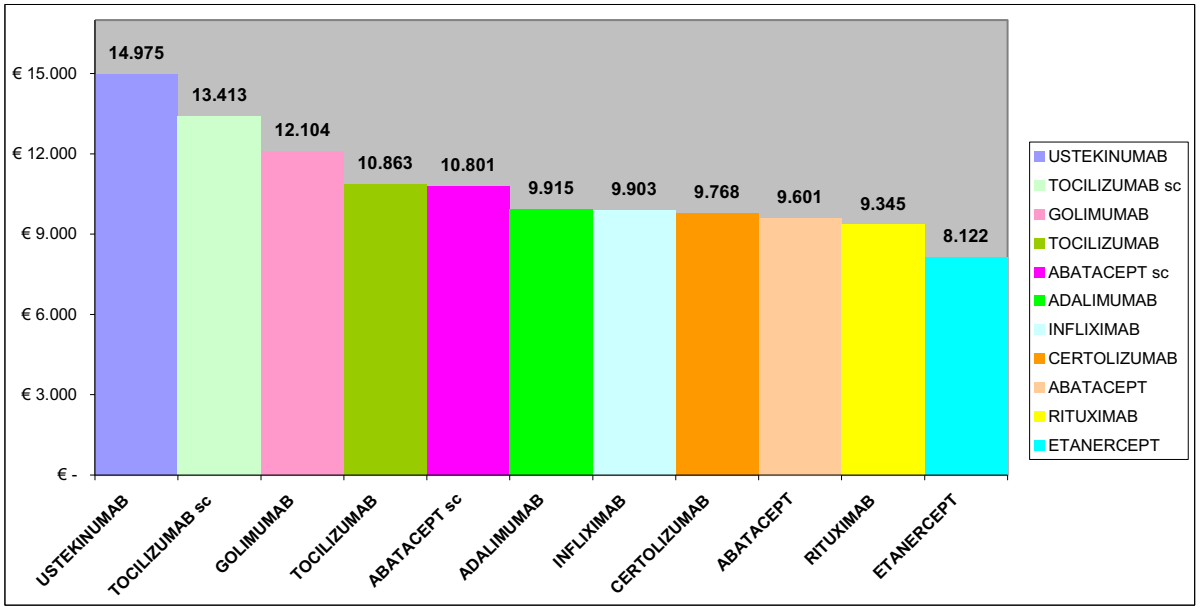
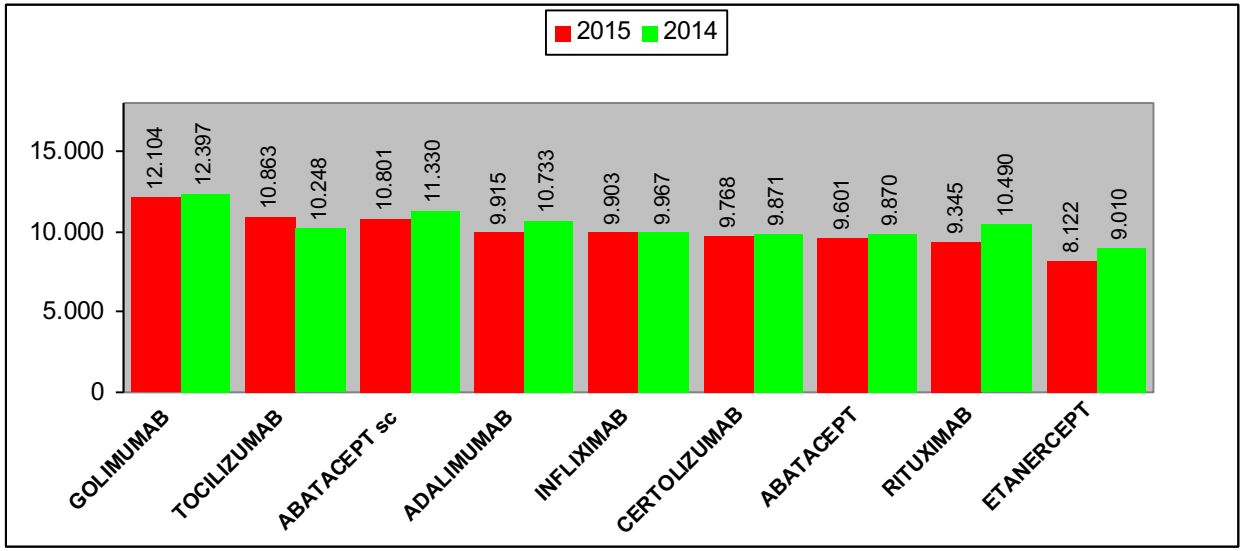
INFLIXIMAB


ASL3 - Costo medio **standard** per farmaco 2015/2014
2015
2014
15.000
10.000
5.000
0
13.217
12.791
12.846
12.846
12.613
13.325
12.471
12.471
12.215
13.693
11.600
11.600
11.566
12.184
10.077
10.218
9.814
9.697
TOCILIZUMAB
GOLIMUMAB
ADALIMUMAB
ABATACEPT sc
ETANERCEPT
RITUXIMAB
ABATACEPT
CERTOLIZUMAB
INFLIXIMAB

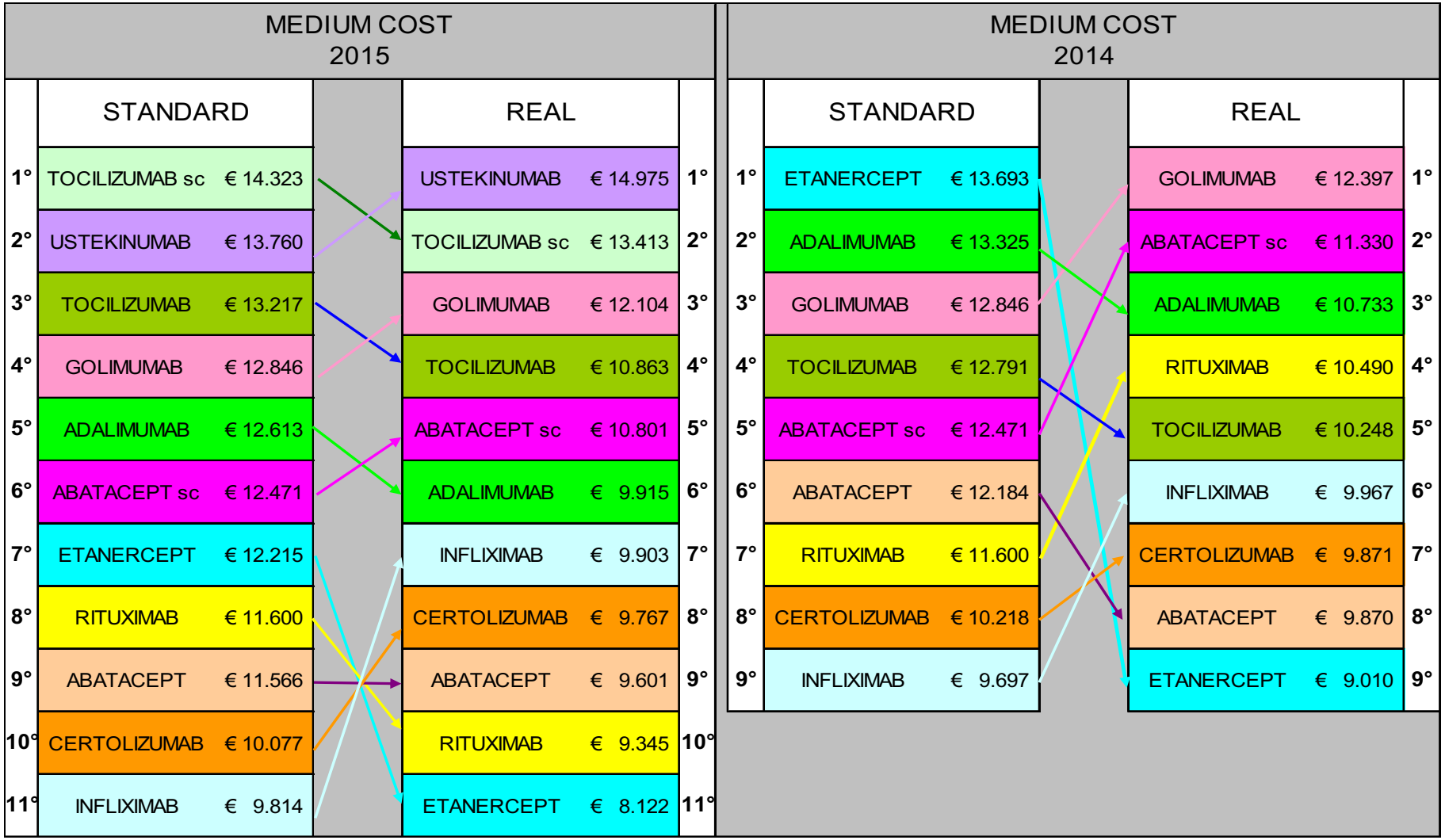
ASL3 - Costo medio **reale** per farmaco - 2015



ASL3 - Costo medio **reale** per farmaco 2015/2014



ASL3 - Costo Medio Standard e Reale per Farmaco
2015 / 2014



ASL3 - Costo Medio Standard e Reale per Farmaco
2015 / 2014

	2015		2014	
ETANERCEPT	1°	€ 8.122	1°	€ 9.010
RITUXIMAB	2°	€ 9.345	6°	€ 10.490
ABATACEPT	3°	€ 9.601	2°	€ 9.870
CERTOLIZUMAB	4°	€ 9.767	3°	€ 9.871
INFLIXIMAB	5°	€ 9.903	4°	€ 9.967
ADALIMUMAB	6°	€ 9.915	7°	€ 10.733
ABATACEPT sc	7°	€ 10.801	8°	€ 11.330
TOCILIZUMAB	8°	€ 10.863	5°	€ 10.248
GOLIMUMAB	9°	€ 12.104	9°	€ 12.397
TOCILIZUMAB sc	10°	€ 13.413		
USTEKINUMAB	11°	€ 14.975		

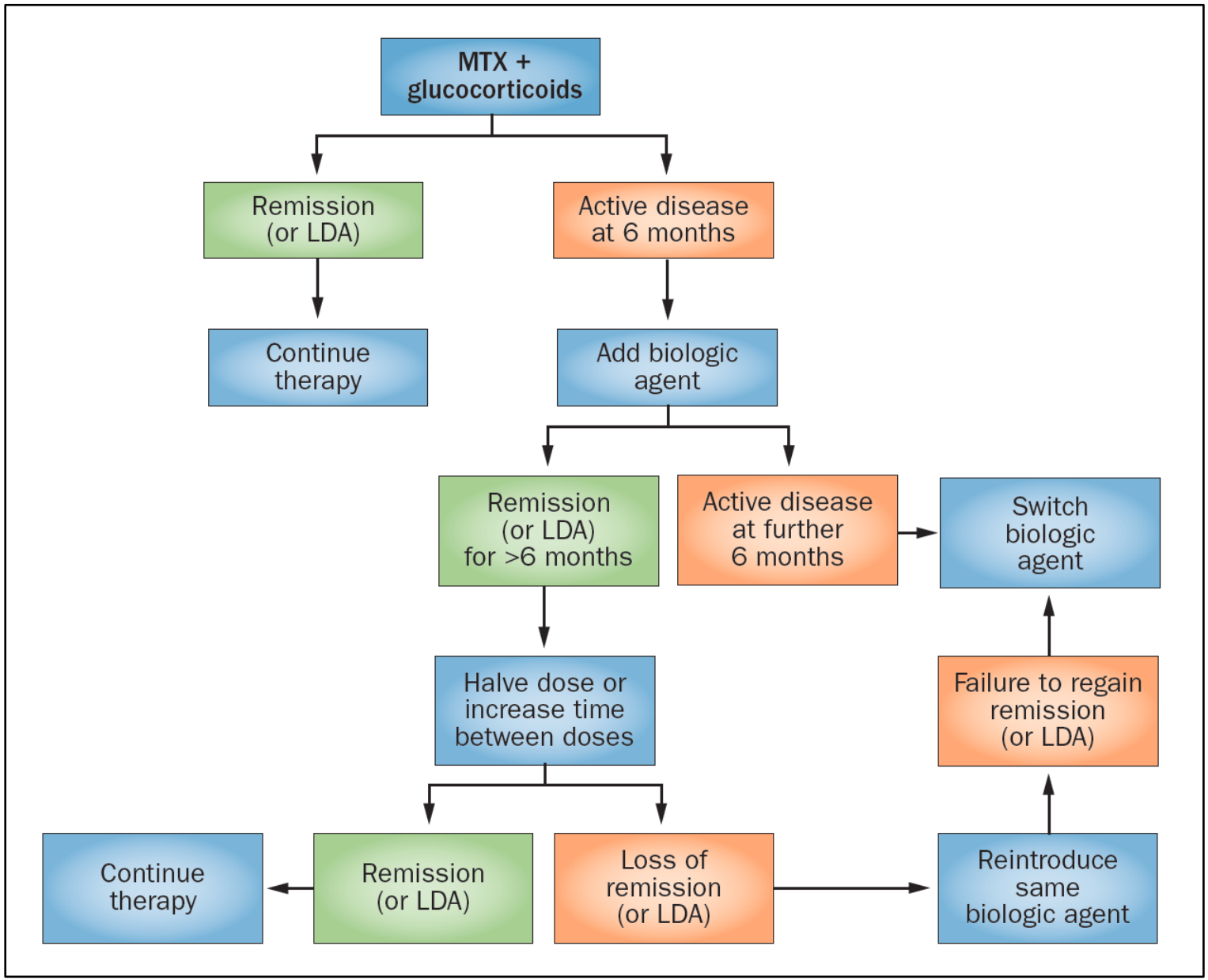
2013 EULAR recommendations for the management of RA with synthetic and biological DMARDs

Management of patients in remission

12.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering biological DMARDs, especially if this treatment is combined with a csDMARD
13.	In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician

Smolen J. et al. Ann Rheum Dis. 2014

Proposed algorithm for withdrawal of biologic therapy in patients with active RA



Smolen J, Aletaha D. Nat Rev Rheumatol 2015

Is Stepdown of biologic treatments really feasible in RA ?

- Discontinuation of biologics is inferior to continuation with respect to disease activity, function and structural outcome.

- Disease activity dose tapering of TNF inhibitors seems slightly inferior to continuation but feasible in most of the patients in persistent remission with no difference on function and short term structural outcome.

- Some predictive factors of persistent remission after dose reduction can be identify:
  - ✓Duration and « quality » of remission
  - ✓Early response to TNFi
  - ✓ACPA /RF negativity
  - ✓Baseline erosion ?

- Good response after restart of TNF inhibitors.

- Limited data on non-TNF biologics.

Combe B. OsteoRheumatology 2015

Flare Rate in Patients with Rheumatoid Arthritis in Low Disease Activity or Remission When Tapering or Stopping Synthetic or Biologic DMARD: A Systematic Review

Conclusion

- One-third of patients with RA with LDA or in remission may taper or stop DMARD treatment without experiencing a disease flare within the first year.
- Dose reduction of TNF blockers results in lower flare rates than stopping and may be noninferior to continuing full dose.
- Radiological progression after treatment deescalation remains low, but may increase slightly.

Kuijper TM et al. J Rheumatol 2015

Review

Are there dangers in biologic dose reduction strategies?

Take home messages

- Dose reduction strategies for biological therapies are being considered as a result of patient choice, reduction of potential dose-dependent risks and to save costs.
- For established disease, cessation of biological therapies is rarely successful and should be avoided.
- **Risks of a dose reduction strategy can include loss of disease control, failure to recapture control after reintroduction of the standard dose and a risk of increased immunogenicity.**
- **Flares of disease may be associated with increased damage (e.g. radiographic or as the result of uncontrolled systemic inflammation such as increased cardiovascular events) and worse patient reported outcomes**.
- When considering dose tapering, care must be taken to reduce the likelihood of flare and subsequent damage by carefully selecting appropriate patients and excluding those with evidence of ongoing disease activity.
- Different approaches may be needed for those with early versus established disease.

Chan CKY et al. Autoimmun Rev 2016

Review

Are there dangers in biologic dose reduction strategies?

- There are **potential dose related risks in not exploring dose reduction** strategies as part of optimising the treatment of patients with inflammatory rheumatic disease.
- These include **the potential risks of leaving individuals with high trough levels of biological therapies on their current doses such as infections or future malignancy.**
- **Dose reduction may also produce significant cost savings** that, if kept within a local rheumatology budget, may justify earlier treatment for patients with lower disease activity or even dose increases when needed.
- Therefore, further studies to elucidate suitable dose reduction strategies and how to accurately identify the most appropriate candidates for reduced dose biologics will continue to be important.

Chan CKY et al. Autoimmun Rev 2016

2016 EULAR Provisional Recommendations

11. If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD.

12. If a patient is in persistent remission, tapering the csDMARD could be considered.

Smolen J. EULAR 2016

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