Optimization of biological drugs in the real clinical life

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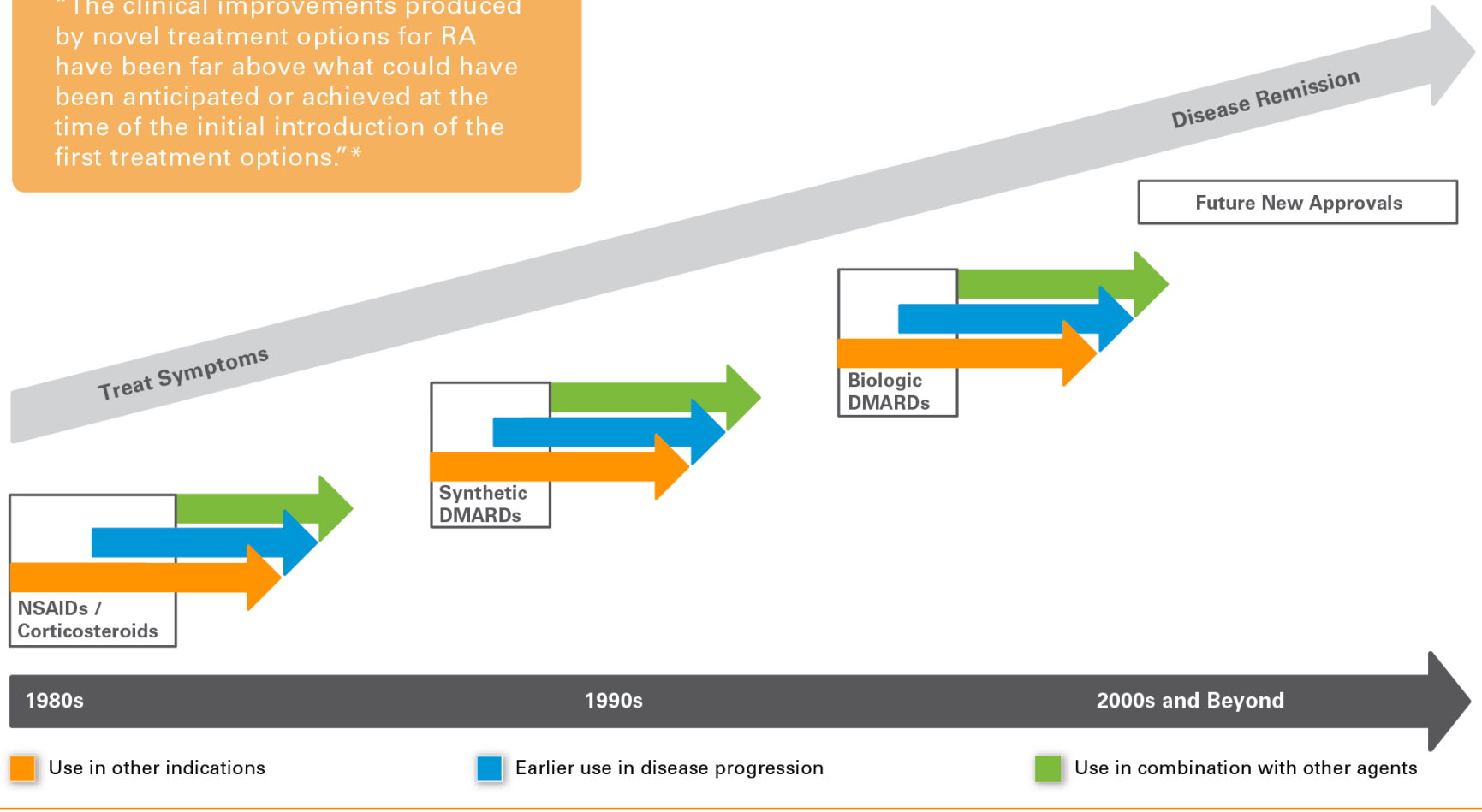
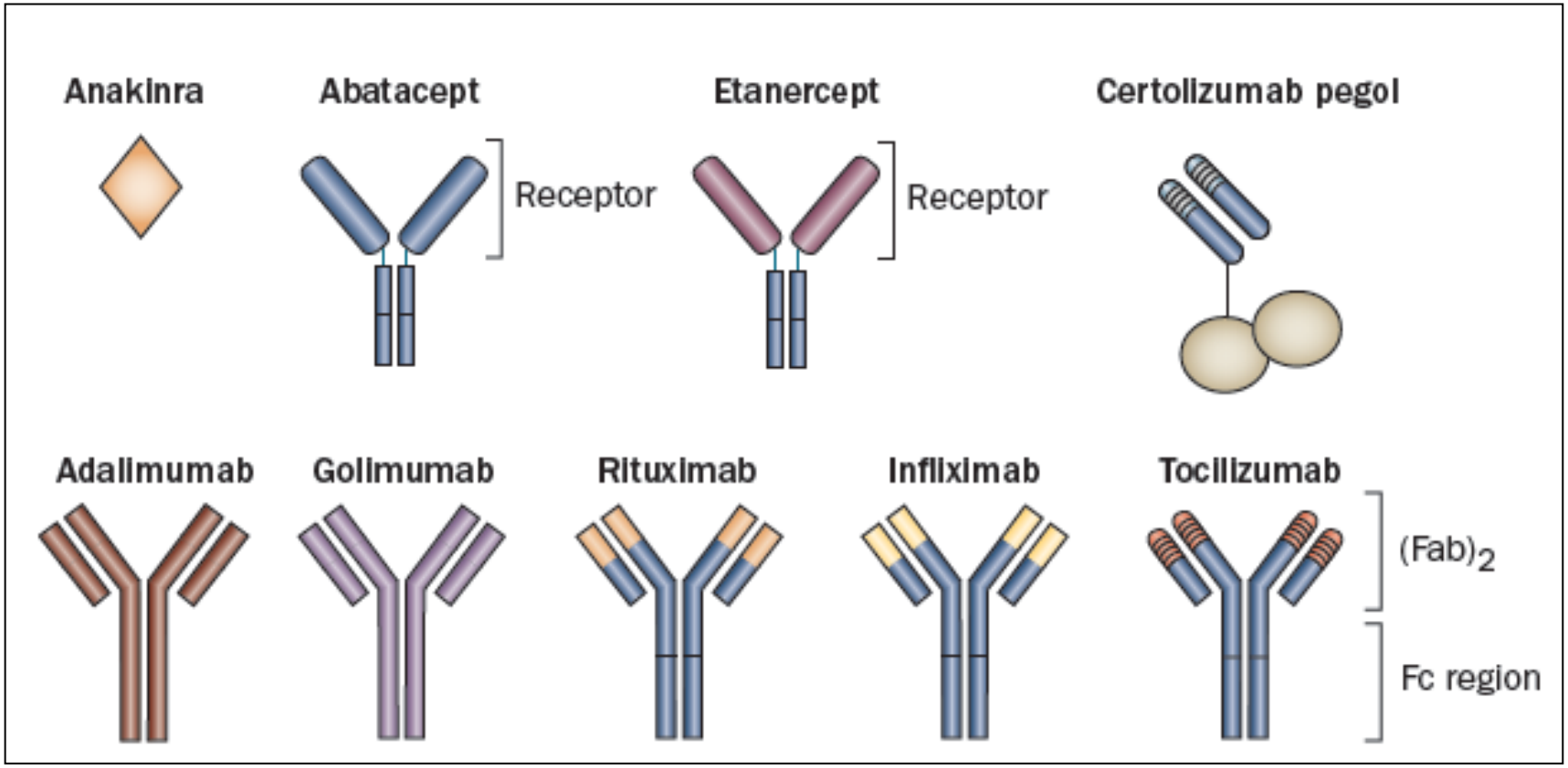
Rheumatoid Arthritis: The Evolution of Clinical Value for Patients

"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

Tools for evaluating RA disease activity

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 and EULAR Improvement Criteria

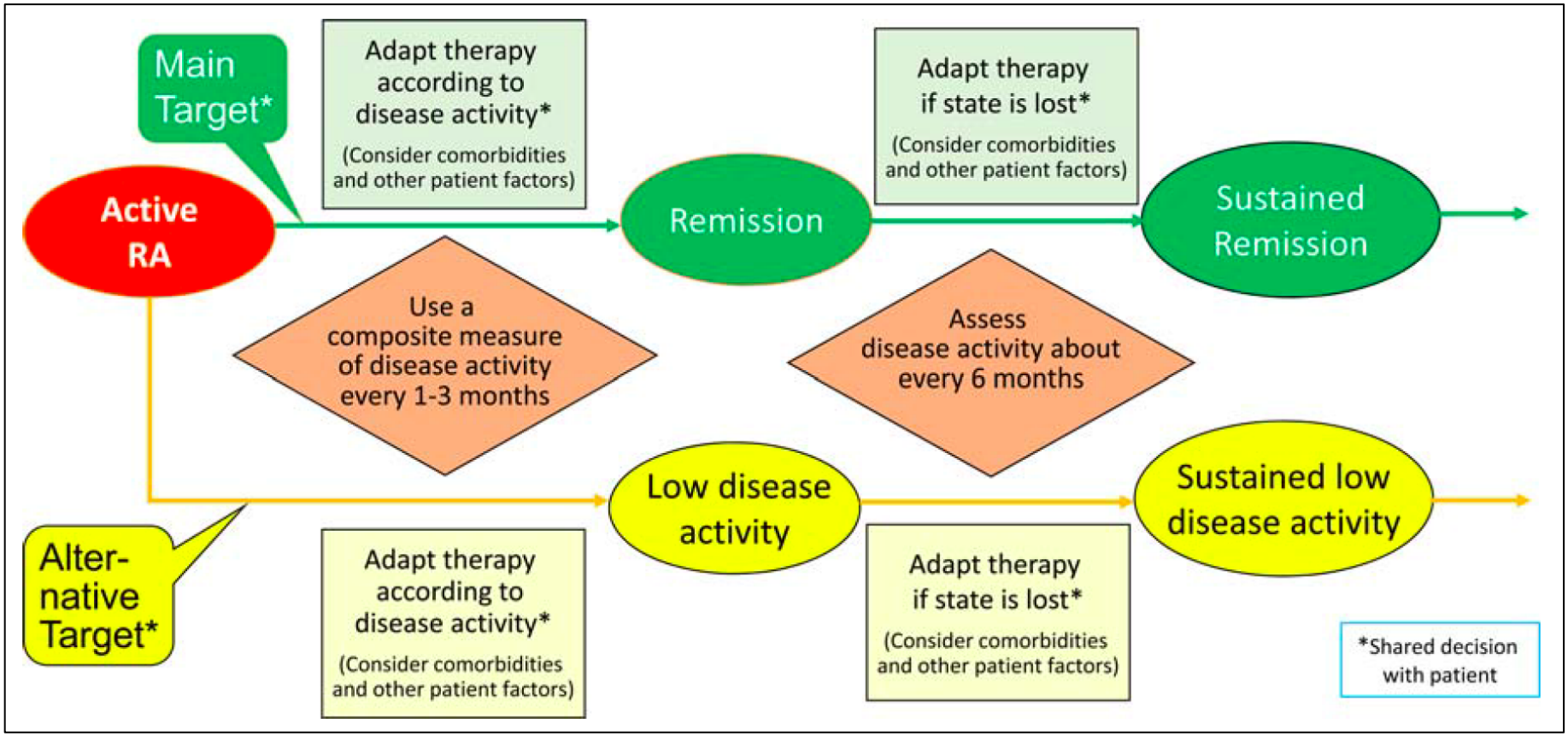
ACR improvement Criteria	
≥ 20% ≥ 50% ≥ 70% improvement in	Tender joint count, and
	Swollen joint count, and
	At least 3 of the following:
	ESR or CRP
	Investigator assessment of global disease activity
	Patient assessment of global disease activity
	Patient assessment of global pain
	Physical disability

EULAR (EULAR28) Response Criteria				
Reached Value		Change in DAS or DAS28 from Baseline		
DAS28	DAS	≤ 0.6	> 0.6 and ≤ 1.2	> 1.2
≤ 3.2	≤ 2.4			***good***
> 3.2 and ≤ 5.1	> 2.4 and ≤ 3.7		***moderate***	
> 5.1	> 3.7	***none***		

Van Gestel AM et al. J Rheumatol 1999

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

ACR-EULAR 2011 Definition of Remission

For clinical trials

- Boolean
  - SJC, TJS, PtGA, CRP all ≤1
- Index-based
  - SDAI ≤3.3

SDAI=SJC+TJC+PhGA+PtGA+ CRP (mg/dl)

For clinical practice

- Boolean
  - SJC, TJC, PtGA all ≤1
- Index-based
  - CDAI ≤2.8

CDAI=SJC+TJC+PhGA+PtGA

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
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Optimization protocol for the use of biological treatments

Year 2014

OPTIMIZATION PROTOCOL: RA – PsA

At each ollow-up visit, if DAS28 <2.6:

- ETA,50 mg every 10 days
- ADA, 40 mg every 3 week
- CER, 200 mg every 3 weeks
- GOL, 50 mg every 5 weeks
- IFX, i.v every 9 weeks
- ABA, every 5 weeks
- TCZ, every 5 weeks
- RTX,every 7 months

After 3 months, in case of no flares:

- ETA,50 mg every 2 weeks
- ADA, 40 mg every 4 weeks
- CER, 200 mg every 4 weeks
- GOL, 50 mg every 6 weeks
- IFX, i.v every 10 weeks
- ABA, every 6 weeks
- TCZ, every 5 weeks
- RTX,every 8 months

After 3 months, if the patient is in remission: TJC $\leq$ 1, SJC $\leq$ 1, CRP $\leq$ 1 mg/dl, PGA $\leq$ 10 mm, or SDAi $\leq$ 3.3.

- ✓ Stop biologic drug and continue cDMARDs on current dose.
- ✓ If patient flares, increase cDMARDS to maximum tolerated dose.
- ✓ In case of no response, restart biologic drug.

OPTIMIZATION PROTOCOL: AS

At each ollow-up visit, if BASDAI <50% of previous value, pain VAS <10, and CRP ≤ 1 mg/dl **:**

- ETA,50 mg every 10 days
- ADA, 40 mg every 3 week
- GOL, 50 mg every 5 weeks
- IFX, i.v every 9 weeks

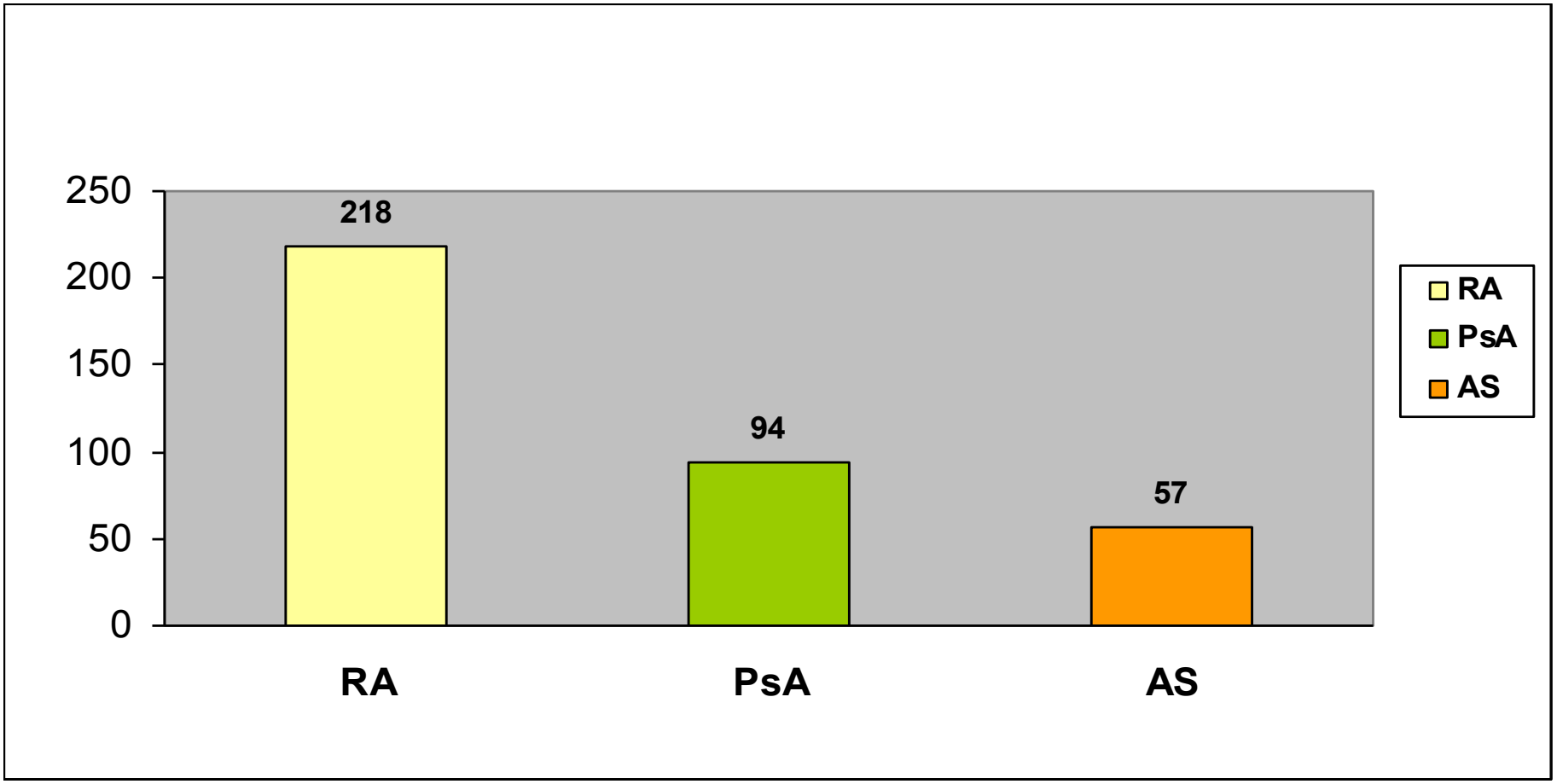
After 3 months, in case of no flares:

- ETA,50 mg every 2 weeks
- ADA, 40 mg every 4 weeks
- GOL, 50 mg every 6 weeks
- IFX, i.v every 10 weeks

After 3 months, if the patient is in remission: BASDAI <50% of previous value, pain VAS <10, CRP and ESR negative.

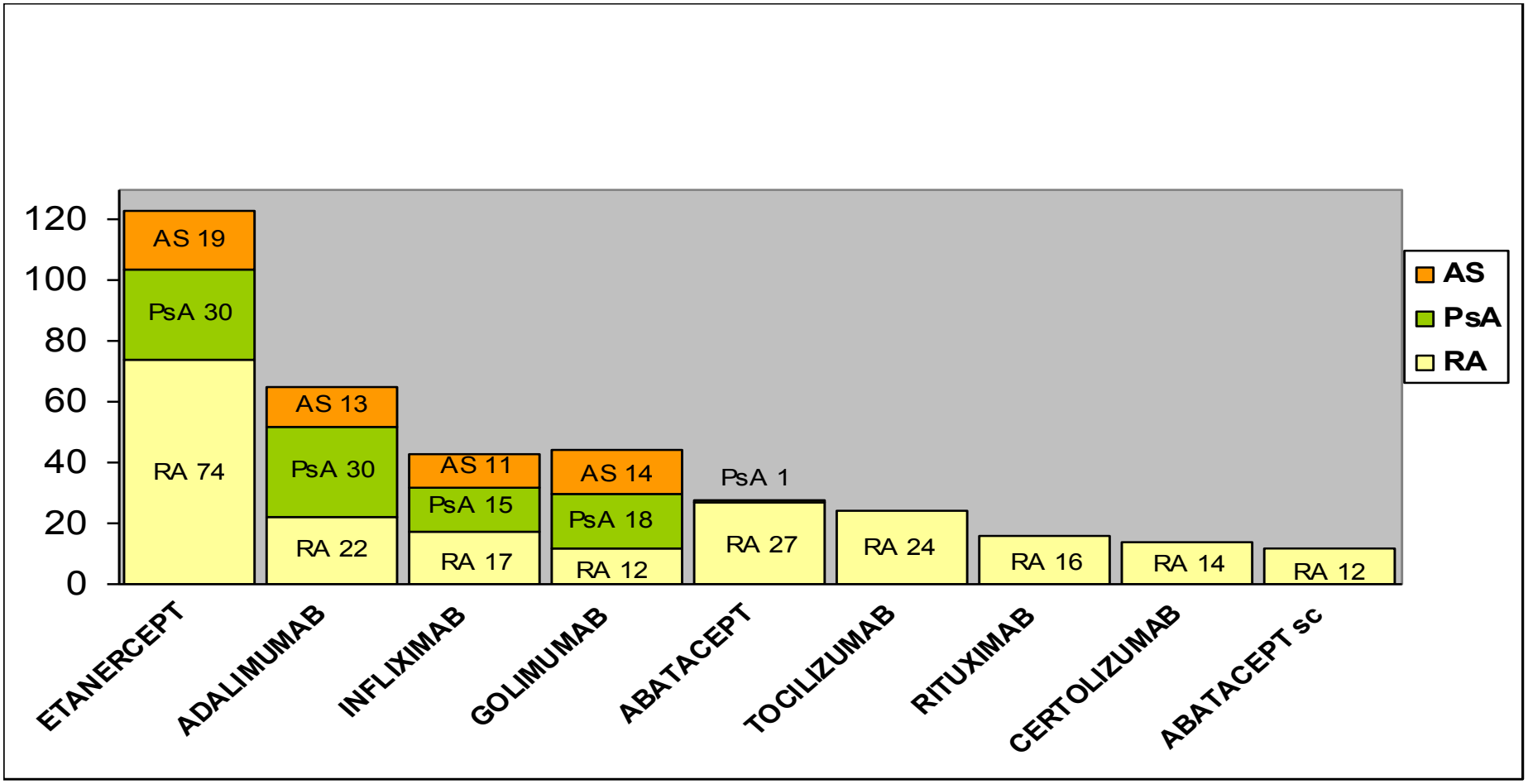
- ✓ Stop biologic drug.
- ✓ If patient flares, restart biologic drug.

Treatments according to Diagnosis



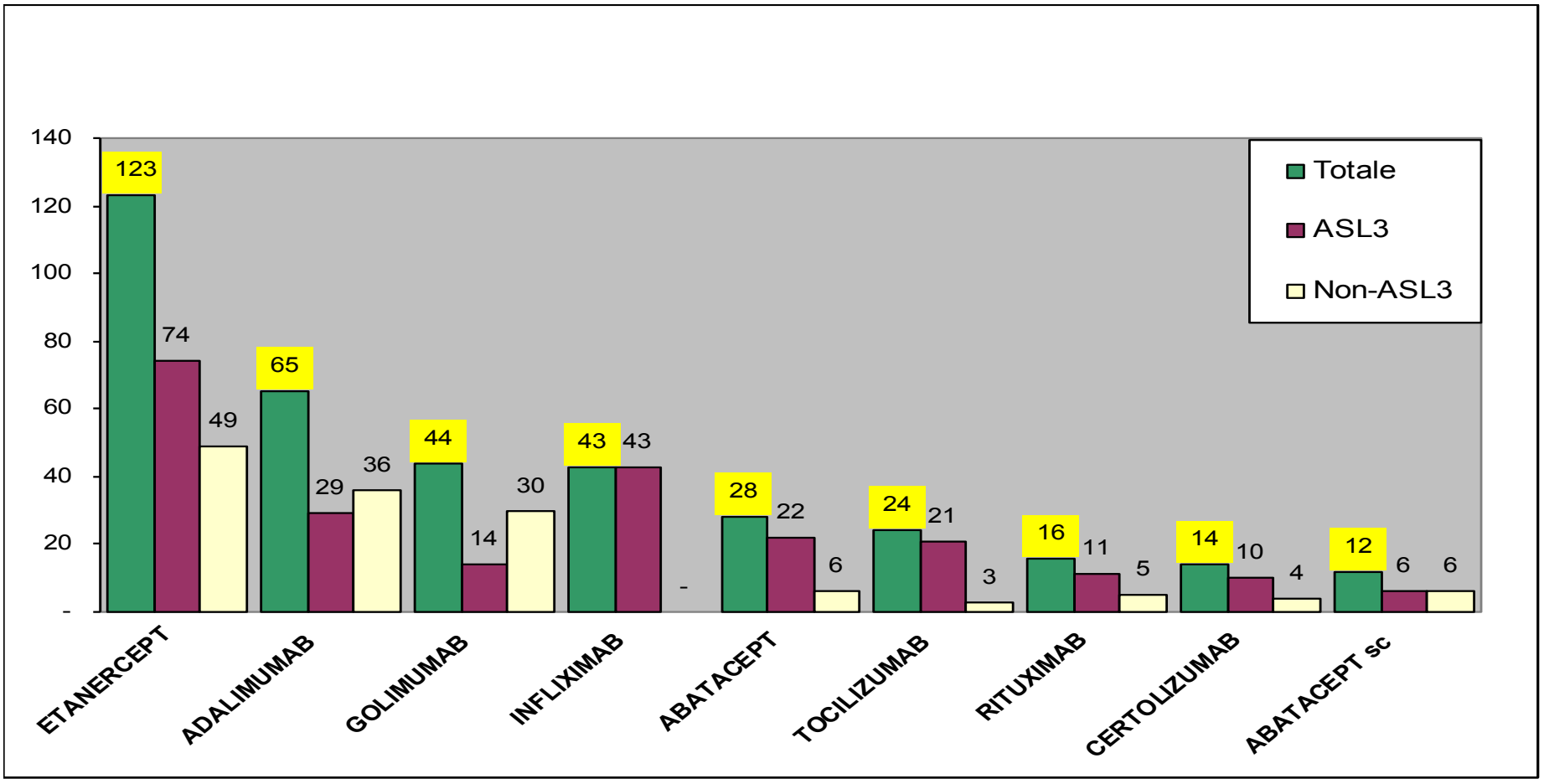
369 treatments (39 switch)

Treatments according to Diagnosis and Drug



N. 369

Treatments according to Diagnosis and Referral



N. 369

Patients provenience:

- ASL3, Genoa area n. 230
- non-ASL3, outside Genoa area n. 139

OPTIMIZATION PROTOCOL
Economic analysis

- **Standard cost**

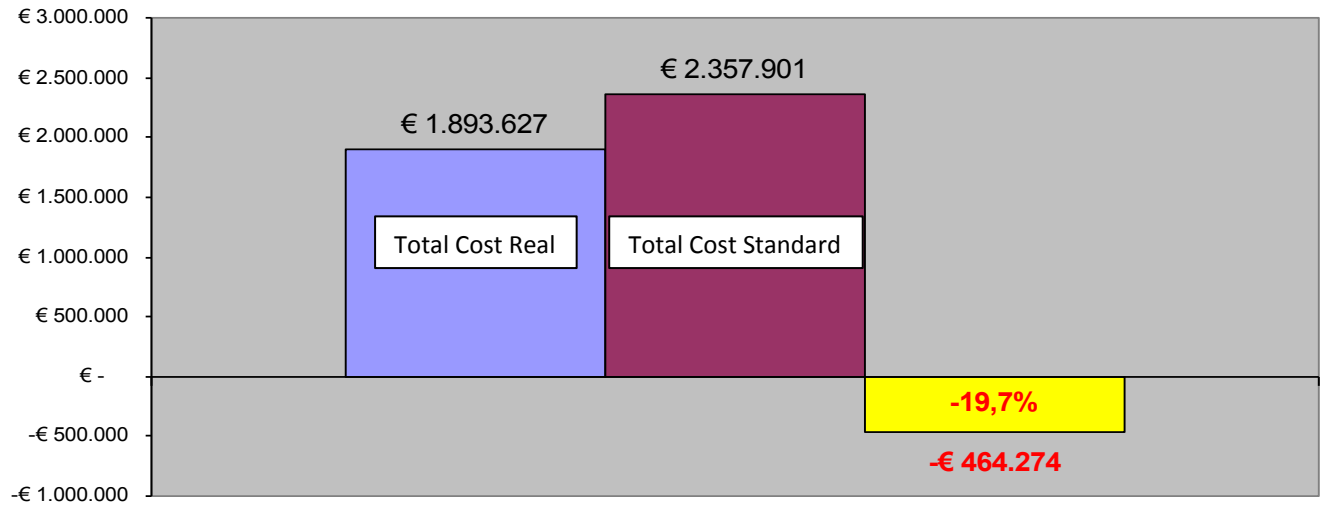
  Drug price according RCPs, multiplied by 52 weeks of treatment.

- **Real cost**

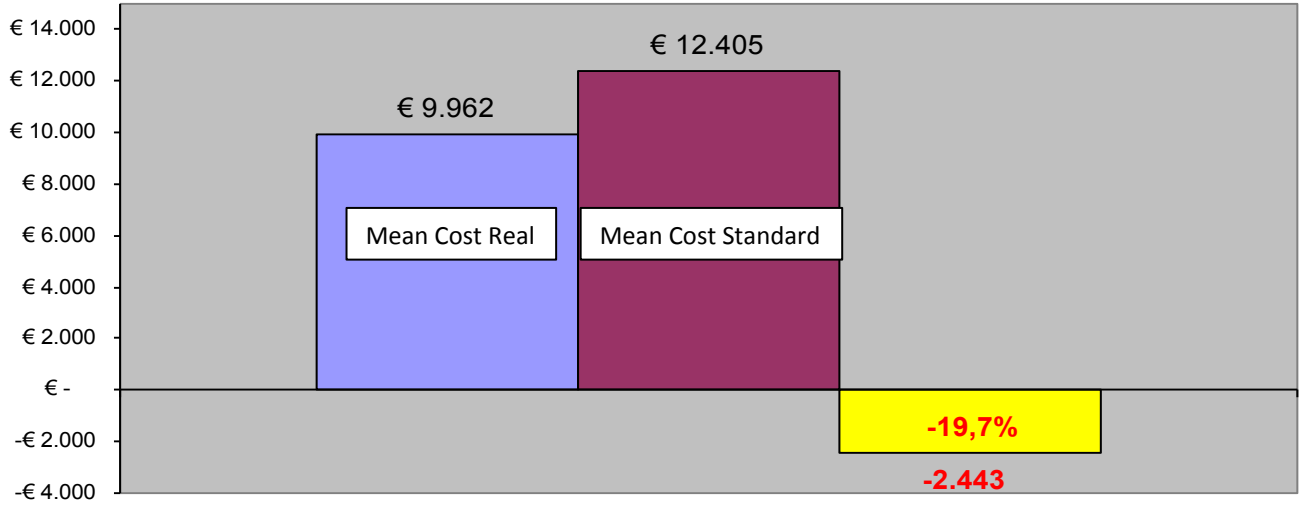
  Effective amount of money spent for each drug on annual basis, inclusive of discount policies.

Analysis limited to ASL3 patients because of accuracy of data

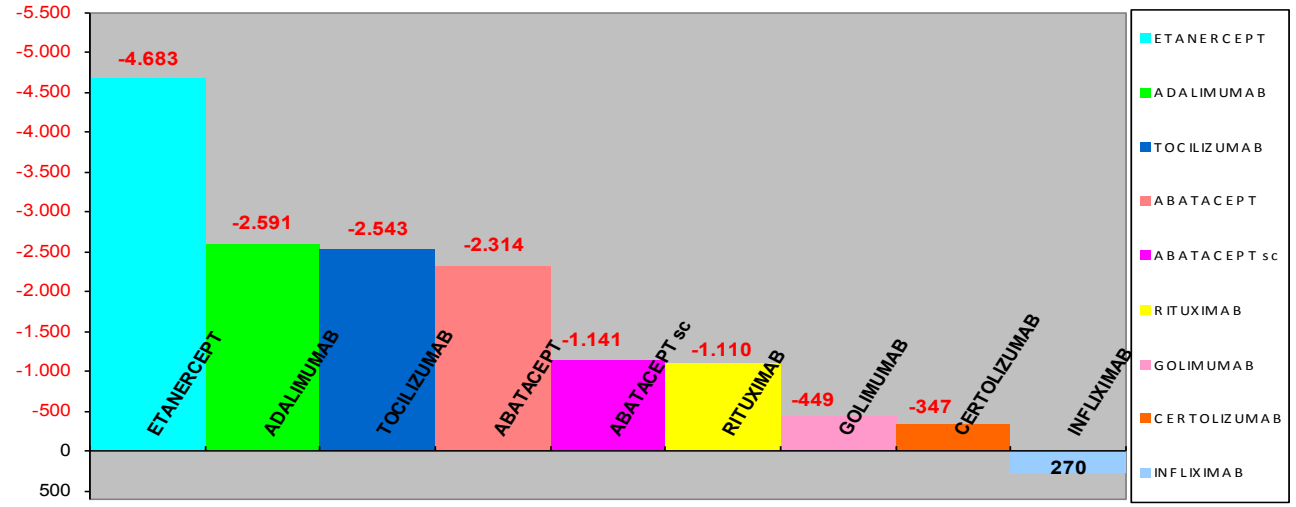
ASL3 – Total Cost (real & standard)



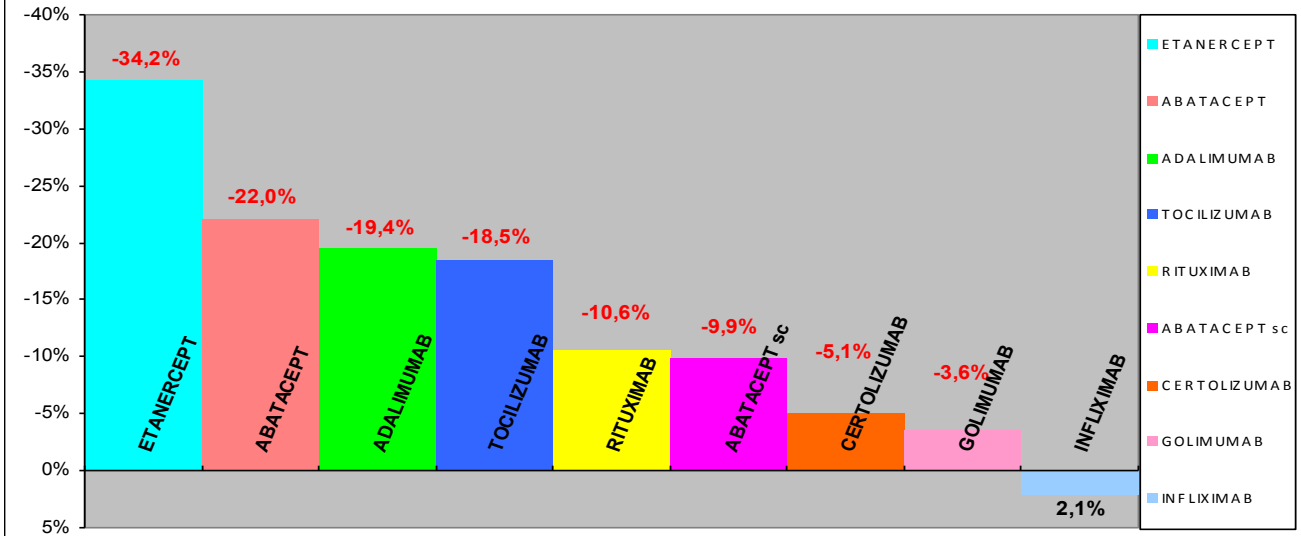
ASL3 – Mean Cost (real & standard)



ASL3 – Drug Cost Difference: Real vs Standard (€)



ASL3 – Drug Cost Difference: Real vs Standard (%)



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

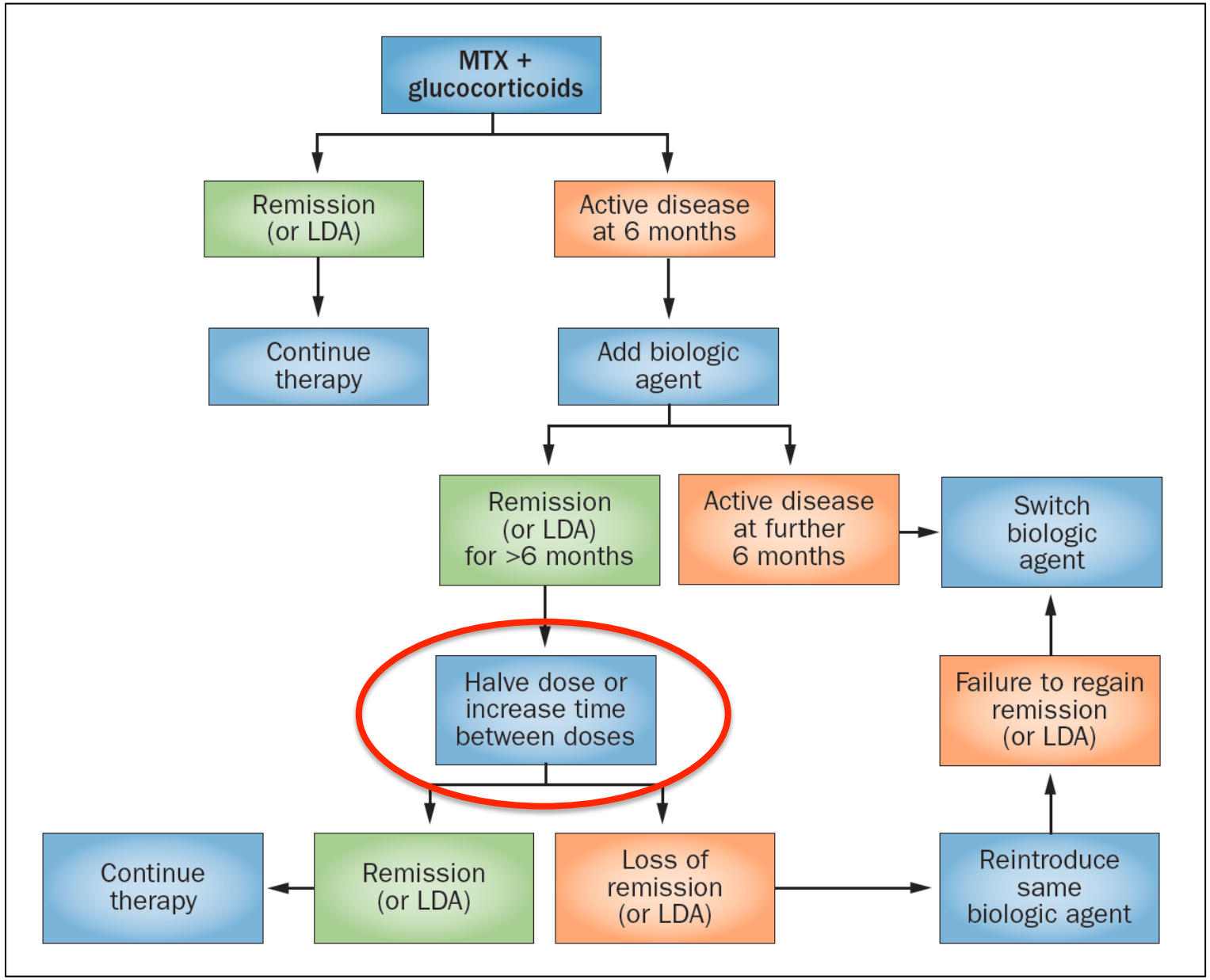
Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges

Key points

- Responses to biologic therapies for rheumatoid arthritis (RA) decrease depending on the patient population: early RA, methotrexate-naive; established RA, methotrexate-experienced; or late RA, anti-TNF experienced
- Within these populations, approved biologic agents that target different molecules have similar efficacy, possibly because they all ultimately inhibit a common pathway, namely proinflammatory cytokines such as TNF or IL-6
- The best outcomes are achieved by timely adaptation or switching of therapies in accordance with disease activity, in a treat-to-target approach, with the aim of remission or at least low disease activity
- Once a good outcome has been reached, reducing the dose or expanding the interval between doses is a feasible approach that enables maintenance of the outcome in most patients
- There exists a 'window of opportunity' soon after symptom onset to prevent the occurrence of damage, but treatment at this stage cannot reverse the disease in most patients
- Reversal of disease might become possible by use of preventative therapies that interfere with the pre-arthritic process before the disease has manifested clinically

Smolen J, Aletaha D. Nat Rev Rheumatol 2015

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

Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial

DRESS Study

WHAT IS ALREADY KNOWN ON THIS TOPIC

Tumour necrosis factor (TNF) inhibitors adalimumab and etanercept are effective in rheumatoid arthritis, but are associated with some side effects and high costs

Dose reduction or stopping (tapering) of TNF inhibitor use is feasible in many patients, although it cannot be predicted which patient can be tapered

In general, disease activity guided strategies to treat rheumatoid arthritis have resulted in optimal clinical outcomes

WHAT THIS STUDY ADDS

A treat-to-target based TNF inhibitor tapering strategy, consisting of increases in intervals between injections until the patient flares or the drug can be stopped, is non-inferior to usual care (a treat-to-target strategy without dose reduction), with regard to occurrence of major flare

Although short lived flares and minimal radiographic progression occurred more frequently with dose reduction, it showed similar outcomes to usual care after 18 months for functioning, quality of life, adverse events, and clinically relevant radiological joint damage

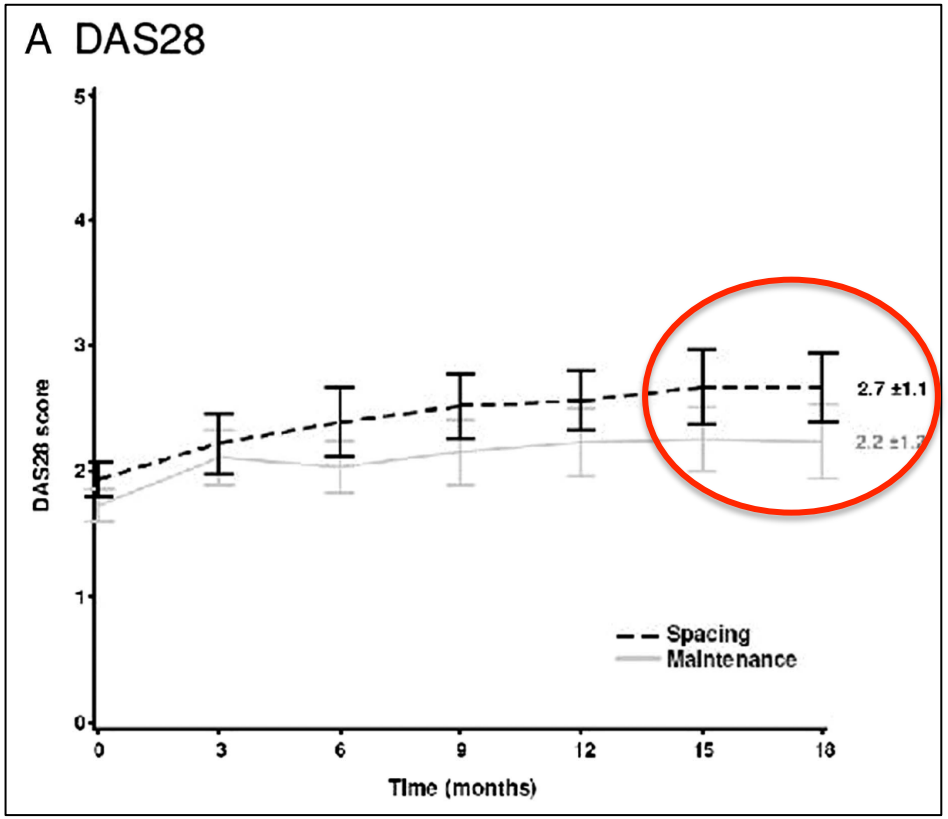
Dose reduction or stopping was successful in two third of patients

van Herwaarden N et al. BMJ 2015

EXTENDED REPORT

Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial *(STRASS: Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study)*

Bruno Fautrel,[1,2] Thao Pham,[3,4] Toni Alfaiate,[5,6] Frédérique Gandjbakhch,[1,2] Violaine Foltz,[1,2] Jacques Morel,[7] Emmanuelle Dernis,[8] Philippe Gaudin,[9] Olivier Brocq,[10] Elisabeth Solau-Gervais,[11,12] Jean-Marie Berthelot,[13,14] Jean-Charles Balblanc,[15] Xavier Mariette,[16,17] Florence Tubach[3,18]



Conclusions

- Tapering was not equivalent to maintenance strategy, resulting in more relapses without impacting structural damage progression.
- Further studies are needed to identify patients who could benefit from such a strategy associated with substantial cost savings.

Fautrel B et al. Ann Rheum Dis 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

Anti-TNF discontinuation and tapering strategies in patients with axial spondyloarthritis: a systematic literature review

Rheumatology key messages

- Published evidence on discontinuation and tapering strategies in axial spondyloarthritis is scarce and weak.
- Discontinuation of anti-TNF therapy in patients with axial spondyloarthritis leads to flare in most cases.
- **Tapering anti-TNF therapy is successful in maintaining low disease activity in most patients with ankylosing spondylitis.**

Navarro-Compan V et al. Rheumatology 2016

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

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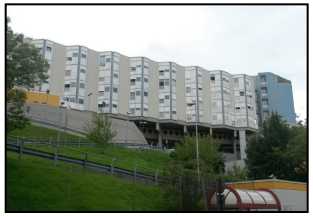
Locations



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