Biologici e biosimilari: problematiche cliniche in reumatologia

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1998-2018
Nuovi farmaci in reumatologia: un ventennio rivoluzionario

Fino al 1998
Terapie tradizionali
(FANS, CS, ICLR, Sali d'Oro, AZA, Cyc, CsA, MTX)

- Controllo attività di malattia: insoddisfacente (necessità di impiego dei CS)
- Non efficacia sulla progressione del danno radiologico
- Invalidità
  Pensioni
  Aumento mortalità

1998-2018
Biologici
Anti-Jak (Small molecules)

- Efficacia sulla attività di malattia: remissione come target possibile (≥50% dei casi)
- Arresto della progressione del danno radiologico
- Funzione mantenuta
  Normale sopravvivenza
  Riduzione costi

....1998

1998-2018

Farmaci biologici approvati per la terapia della AR

Farmaco	Target	Posologia	Indicazioni
Adalimumab	TNFa	40 mg/sc/2 sett.	AR, AP, SA
Adalimumab biosimil.	TNFa	40 mg/sc/2 sett.	AR, AP, SA
Certolizumab	TNFa	200 mg/sc/2 sett.	AR (AP, SA)
Etanercept	TNFa	50 mg/sc/sett.	AR, AP, SA
Etanercept biosimil.	TNFa	50 mg/sc/sett.	AR, AP, SA
Golimumab	TNFa	50 mg/sc/mese	AR, AP, SA
Infliximab	TNFa	3-5 mg/Kg/ev/8 sett.	AR, AP, SA
Infliximab biosimil.	TNFa	3-5 mg/Kg/ev/8 sett.	AR, AP, SA
Tocilizumab	IL-6	8 mg/Kg/ev/4 sett. 162 mg/sc/sett.	AR
Sarilumab	IL-6	200 mg/sc/2 sett.	AR
Rituximab	CD-20	1000 mg/ev/6 mesi	AR
Rituximab biosimil.	CD-20	1000 mg/ev/6 mesi	AR
Anakinra	IL-1	100 mg/sc/die	AR
Abatacept	CD28	750 mg/ev/4 sett. 125 mg/sc/sett.	AR

Targeted synthetic DMARDs
-Baricitinib: anti-JAK 1-2
-Tofacitinib: anti-JAK 1.3

Anti-TNFs

Non anti-TNFs

Terapie di seconda linea approvate per la PsA e SpA

Biosimilars

Definition

A biosimilar medicine ('biosimilar') is a medicine highly similar to another biological medicine already marketed in the EU (the so-called 'reference medicine')

A biosimilar is not regarded as a generic of a biological medicine. This is mostly because the natural variability and more complex manufacturing of biological medicines do not allow an exact replication of the molecular microheterogeneity.

www.ema.europa.eu/docs/en_GB/.../05/WC500226648.pdf. April 27, 2017.

Biosimilari: RCTs in Reumatologia

- Bio-Infliximab: Artrite reumatoide, Spondilite anchilosante
- Bio-Adalimumab: Artrite reumatoide
- Bio-Etanercept: Artrite reumatoide

Comparabile efficacia, immunogenicità, and sicurezza rispetto al biologico originale di riferimento

Biosimilari in reumatologia: problematiche aperte di maggior rilievo

- Estrapolazione delle indicazioni (Extrapolation): approvazione per tutte le indicazioni rilasciate al biologico referente.
- Non-medical switching da originator a biosimilare
- Non-medical switching tra biosimilari

Non-medical switching
Definizione

- ✓ Il Non-medical switching consiste nel trattare un paziente con il biosimilare sostituendolo al biologico originale che comunque si era dimostrato efficace. In considerazione del più basso costo dei biosimilari, la ragione di tale procedura è di solito economica.

Intercambiabilità:

- ✓ **EMA:** the possibility to switch from the originator to the respective biosimilar or viceversa
- ✓ **FDA:** An interchangeable product is required to meet additional requirements that go beyond biosimilarity to demonstrate that it is expected to produce the same clinical result as the originator product in any given patient and, for products that are administered more than once, that no risks exist in terms of safety or decreased efficacy when alternating or switching between the originator and biosimilar products.

Secondo Position Paper AIFA sui Farmaci Biosimilari

In Italia la posizione dell'AIFA chiarisce che i medicinali biologici e biosimilari non possono essere considerati *sic et simpliciter* alla stregua dei prodotti generici, o equivalenti.

Pur considerando che la scelta di trattamento rimane una decisione clinica affidata al medico prescrittore, a quest'ultimo è anche affidato il compito di contribuire a un utilizzo appropriato delle risorse ai fini della sostenibilità del sistema sanitario e la corretta informazione del paziente sull'uso dei biosimilari.

Come dimostrato dal processo regolatorio di autorizzazione, il rapporto rischio-beneficio dei biosimilari è il medesimo di quello degli originatori di riferimento. Per tale motivo, l'AIFA considera i biosimilari come prodotti intercambiabili con i corrispondenti originatori di riferimento. Tale considerazione vale tanto per i pazienti *naïve* quanto per i pazienti già in cura.

Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases

Ann Rheum Dis 2017

Jonathan Kay,[1] Monika M Schoels,[2] Thomas Dörner,[3] Paul Emery,[4] Tore K Kvien,[5] Josef S Smolen,[2,6] Ferdinand C Breedveld,[7] on behalf of the Task Force on the Use of Biosimilars to Treat Rheumatological Diseases

1.	The availability of biosimilars must significantly lower the cost of treating an individual patient and increase access to optimal therapy for all patients with rheumatic diseases.	100	5	D
6.	Currently available evidence indicates that a single switch from a bio-originator to one of its biosimilars is safe and effective; there is no scientific rationale to expect that switching among biosimilars of the same bio-originator would result in a different clinical outcome but patient perspectives must be considered.	96	1b	A
7.	Multiple switching between biosimilars and their bio-originators or other biosimilars should be assessed in registries.	100	5	D
8.	No switch to or among biosimilars should be initiated without the prior awareness of the patient and the treating healthcare provider.	91	5	D

Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?

We read with interest the recently published recommendations for the use of biosimilars in rheumatology practice.[1] However, we have some concerns regarding recommendation 6 on the efficacy and safety of switching from the originator biologic to the respective biosimilar. Considering the strong impact of the European League Against Rheumatism recommendations on real-life clinical decisions, such recommendation seems not sufficiently supported by the evidence because available data do not allow to draw definitive conclusion on the switching strategy. To date, the efficacy and safety of infliximab and etanercept biosimilars in substitution of the bio-originators have been assessed in four long-term extension reports following the blinded phase of the respective randomised controlled trials (RCTs),[2–5] but the transposition of these results to the real-life practice seems rather questionable. Indeed, patients treated in the setting of real-world practice greatly differ from those enrolled in clinical trials, as suggested by an analysis from the German RABBIT registry showing that only 21%–33% of the included patients would have been eligible for RCTs.[6] Also the results of the NOR-SWITCH trial do not adequately support the switching strategy from infliximab originator (re-IFX) to infliximab biosimilar (bio-IFX) in patients with inflammatory rheumatic diseases because only 198 (41%) out of 481 enrolled patients had a rheumatic disorder, including 91 (18.9%) spondyloarthritis (SpA), 77 (16%) rheumatoid arthritis (RA) and 30 (6.2%) psoriatic arthritis (PsA).[7] Consequently, the study lacks of statistical power with important repercussion on the clinical significance of the results in patients with SpA, RA and PsA. The DANBIO registry reported data from a large series of 802 patients with RA, SpA and PsA who were switched from re-IFX to bio-IFX.[8] No negative impact of bio-IFX on the disease activity was recorded, but the retention rate was significantly lower as compared with a historical cohort of patients receiving re-IFX (86.8% vs 83.4%; P: 0.03). Similar findings have been recently observed in other clinical series from Turkey.[9]

Data from the DANBIO registry on the switching from originator etanercept (re-ETN) to biosimilar etanercept (bio-ETN) were recently presented.[10] At the end of the follow-up period, bio-ETN was withdrawn in 129 (8.3%) out of 1548 patients who were in clinical remission prior to the switching. Confirming the different clinical characteristics of patients treated in real-life practice, despite a shorter follow-up duration of 5 months, the percentage of withdrawals was higher than in the study of Emery and colleagues[4] (5% over 48 weeks). In this sense, the paucity of data from real life and the absence of controlled trials suggest that also recommendation 7 (evidence level 5 and degree of recommendation D)[1] may be misleading for clinicians, who may be driven by health authorities to choices made only on an economic basis.

To conclude, in our opinion, available data from real-world clinical practice, somewhat conflicting with those of RCTs, seem to suggest that it is premature to formulate recommendations on the switching strategy from the bio-originator to its biosimilar.

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«To conclude, in our opinion, available data from real-world clinical practice, somewhat conflicting with those of RCTs, seems to suggest that is premature to formulate recommendations on the switching strategy from the bio-originator to its biosimilar.»

Real-life studies on switching from originator to biosimilar

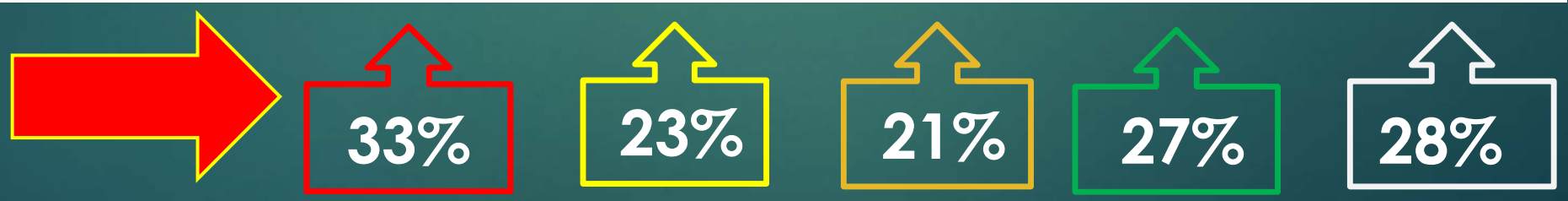
Effectiveness of Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis in an Observational Cohort Study

Comparison of Patients According to Their Eligibility for Major Randomized Clinical Trials

Zink A, et al. Arthritis Rheum 2006

Table 1. Baseline characteristics of the patients according to their eligibility for the major randomized controlled trials*

	Eligible by inclusion criteria of ATTRACT trial		Eligible by inclusion criteria of Moreland et al trial		Eligible by inclusion criteria of TEMPO trial		Eligible by inclusion criteria of ARMADA trial		Eligible by inclusion criteria of van de Putte et al trial	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
No. of patients	101	271	149	498	134	384	119	320	123	316



Aaltonen KJ, et al. Rheumatology 2017: **Only 7.6-44% of the patients would have been potentially eligible for the RCTs.**

Real-life non-medical switching from originators to the respective biosimilars

Author/year	Drug	Disease	Pts n°	Follow-up/mo	Discontin.N (%)
Glintborg 2017	Bio-IFX	RA,PsA,SpA	802	12	132 (16.4%)
Nikiphorou 2015	Bio-IFX	RA,PsA,SpA	39	11	11 (28%)
Benucci 2017	Bio-IFX	SpA	41	6	1 (2.4%)
Gentileschi 2016	Bio-IFX	RA,PsA,SpA	23	2	7 (30.4%)
Abdalla 2017	Bio-IFX	RA,PsA,SpA	34	6	5 (14.7%)
Tweehuysen ACR-2017	Bio-IFX	RA,PsA,SpA	192	6	44 (22.9%)
Yazici ACR 2016	Bio-IFX	RA,SpA,PsA	213	9	134 (62.9%)
Scherlinger 2017	Bio-IFX	RA,PsA,SpA	89	8	25 (28%)
Avouac 2018	Bio-IFX	RA,SpA	260	9	59 (22.6)
Joseph EULAR 2017	Bio-IFX	RA,PsA,SpA	160	12	48 (30%)
Hoiroyd EULAR 2017	Bio-ETN	RA,PsA,SpA	68	6	8 (11.7%)
Alten ACR 2017	Bio-ETN	RA	2938	2	323 (11%)
Hendricks ACR 2017	Bio-ETN	RA,SpA	85	4	9 (10.5%)
Dyball ACR 2017	Bio-ETN	RA	38	7	6 (16.8%)
Tweehuysen ACR-2017	Bio-ETN	RA,PsA,SpA	635	6	60 (10%)

Baseline disease activity: Remission (DAS28<2.6) or LDA (DAS28<3.2)

Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial

Lancet 2017

Kristin K Jørgensen, Inge C Olsen*, Guro L Goll*, Merete Lorentzen*, Nils Bolstad, Espen A Haavardsholm, Knut E A Lundin, Cato Mørk†, Jørgen Jahnsen†, Tore K Kvien†, on behalf of the NOR-SWITCH study group*

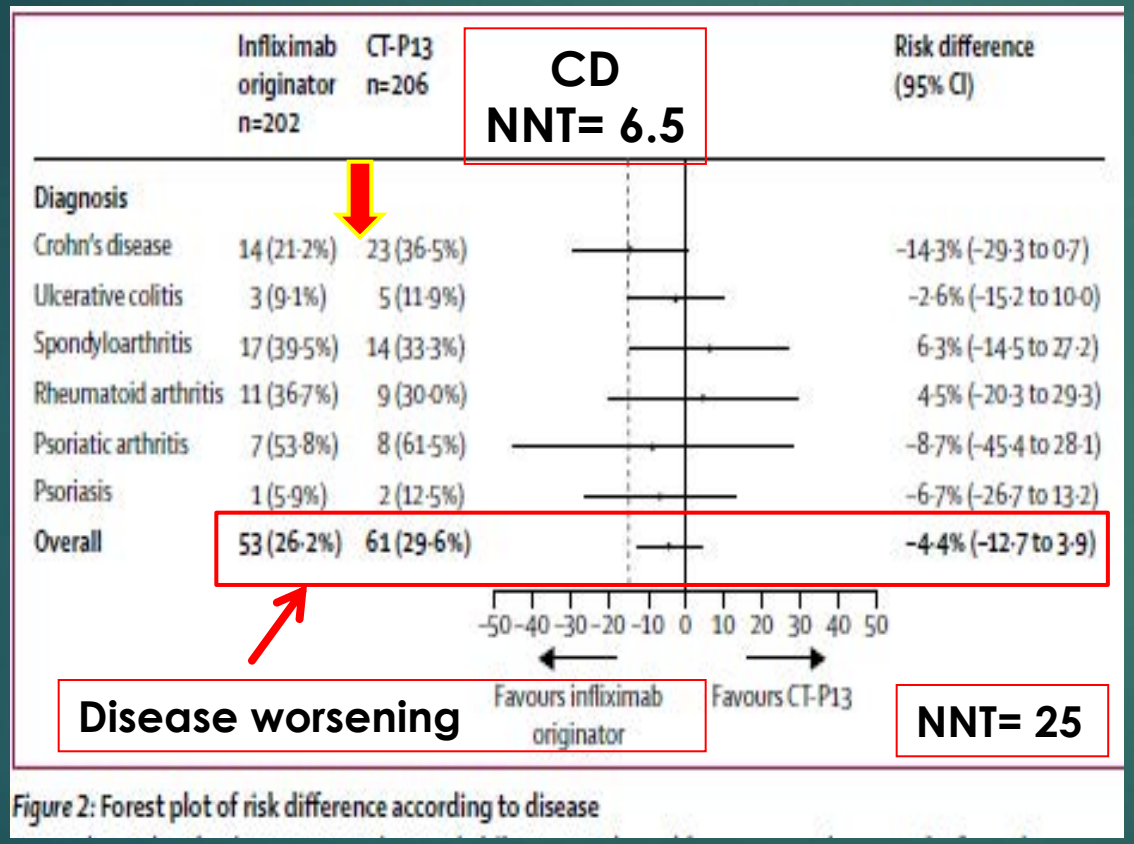


Figure 2: Forest plot of risk difference according to disease

CD= 155 (32%) pts
UC= 93 (19%) pts.
SpA= 91 (19%) pts.
RA= 77 (16%) pts.
PsA= 30 (6%) pts.
Pso= 35 (7%) pts

Terapia stabile con re-IFX da 6 mesi

Non-inferiority cut-off: 15%

The study was not powered for non-inferiority in individual diseases

Annals of the
RHEUMATIC DISEASES
The Eular Journal

Nocebo effect

Seeing the glass either half full or half empty: response to the correspondence "Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?"

Journal:	*Annals of the Rheumatic Diseases*
Manuscript ID	annrheumdis-2018-213021
Article Type:	Correspondence
Date Submitted by the Author:	15-Jan-2018
Complete List of Authors:	Scherlinger, Marc; Centre Hospitalier Universitaire de Bordeaux, Rheumatology Schaeverbeke, Thierry; CHU Bordeaux, Rheumatology
Keywords:	DMARDs (biologic), Inflammation, Disease Activity

These results strongly suggest that the lower retention rate after the switch is due to a nocebo effect,[7] or an incorrect attribution bias where a random flare-up is falsely attributed to an unrelated factor (e.g. the switch).

Thus, one can see the glass half full or half empty. We prefer to see evidence that in case of switch, 70% of patients will remain treated with the biosimilar leading to substantial savings for the health system, and that the other 30% will either switch back to the originator or to another biologic.

Summary
Unclarified issues of nocebo in rheumatology.

Definition

- Generic: subjective reaction opposite to placebo effect.
- Neurochemical and neuroimaging features non included.

Diagnosis

- Substantially a diagnosis of exclusion.
- Lack of classification criteria e outcome measures.
- Several nocebo-related symptoms may be objectivized.

Pathogenesis

- Whether the pathophysiology resulting from studies on healthy subjects, and in neurology may be applied in rheumatic disorders remains to be demonstrated.
- The complexity of pain mechanisms in RA may activate different nociception pathways.

Trials of switching

- Nocebo-attributed discontinuations are entrusted to the individual clinician decision.
- Absence of neurochemical, and neuroimaging studies in rheumatology field.
- Substantial absence of data on drug and TNF levels in studies of nocebo-attributed discontinuations.
- At least in part, nocebo diagnosis may be due to real drug failure.

Biosimilari in Artrite Psoriasica

Biosimilari in Artrite psoriasica

- By extrapolation of indications, anti-TNF biosimilars were approved for the treatment of PsA.
- In absence of specific trials, data of efficacy of biosimilars CT-P13 and SB4 were retrieved from PsA subgroups of studies on different inflammatory disorders.
- In 30 PsA patients enrolled in the NOR-SWITCH trial, CT-P13 did not reach the -15% non-inferiority cut-off of clinical equivalence.
- Overall, in comparison with the originators, a trend to a lower efficacy, and a higher discontinuation rate resulted in PsA patients receiving CT-P13 and SB4. (Giunta A, et al. Br J Dermatol 2019; Bonifati C, et al. J Dermatolog Treat 2019; Pescitelli L, et al. Int J Clin Pharm 2019)
- The few available data, and the low grade of evidence do not allow to draw conclusive remarks, hence specific studies are required.

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Switch da originale a biosimilare 2018-2019

-Infliximab biosim.: 76 paz. ; Abbandoni: 15 paz. (19,7%); Nocebo (?): 2 paz. (13,3%)

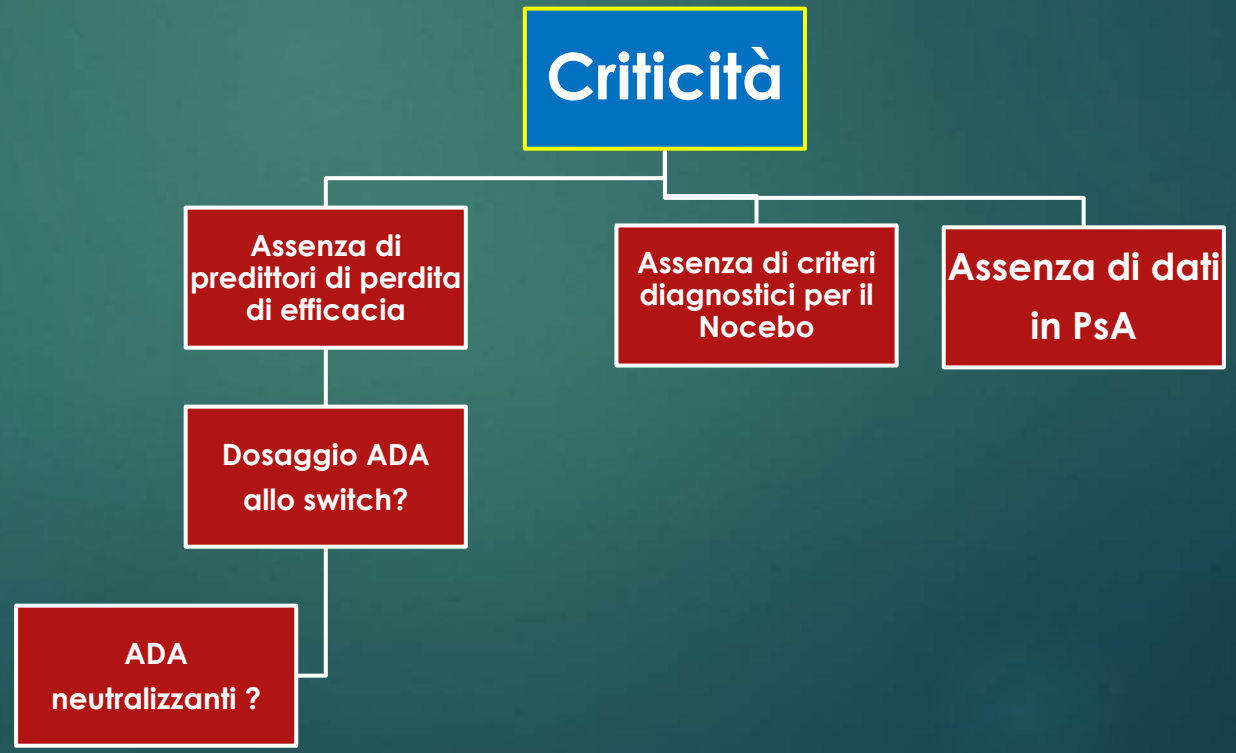
-Etanercept biosim.: 192 pz.; Abbandoni: 41 (21,3%); Nocebo (?): 3 paz. (7,3%)

-Adalimumab biosim.: 186 paz.: Abbandoni: 35 (18,8%); Nocebo (?): 1 paz. (2,8%)

Dati nella media riportata in letteratura

MEDICINALI BIOSIMILARI
Analisi di sicurezza

12/07/2019



AIFA
AGENZIA ITALIANA DEL FARMACO

Biosimilari in Reumatologia
Conclusioni

- Evidenza scientifica di efficacia e sicurezza nei pazienti naïve derivante dai RCTs
- Evidenza di basso livello scientifico relativa allo switch da originator a biosimilare
- Assenza di studi specifici di switch nelle singole patologie nella real-life
- Dati di peso scientifico molto limitato in pazienti con artrite psoriasica
- Necessità di indicatori prognostici positivi per la selezione dei pazienti candidati allo switch
- Necessità di criteri per la diagnosi di «effetto «nocebo»