Biologici in Reumatologia

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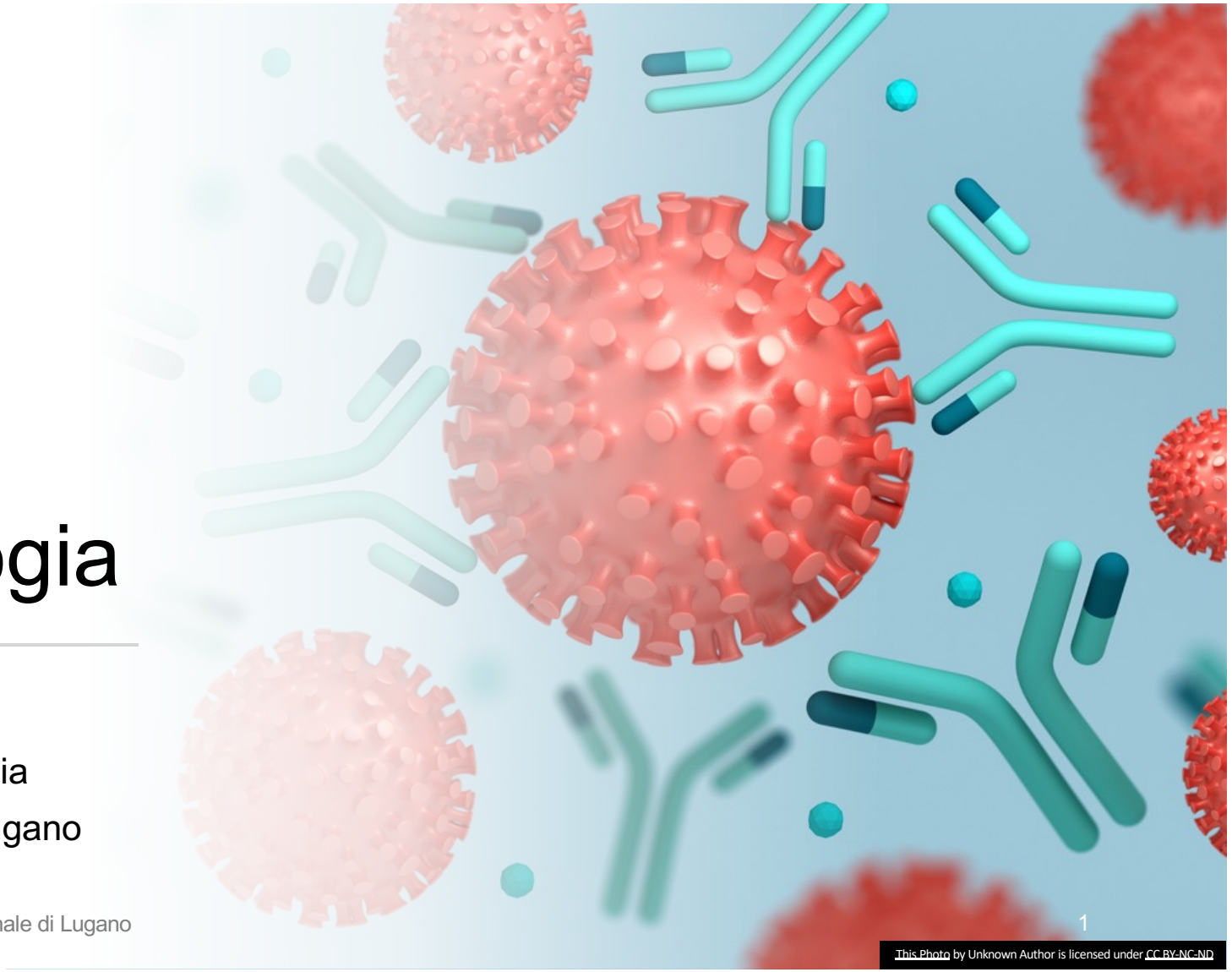


Che cosa sono i Biologici?

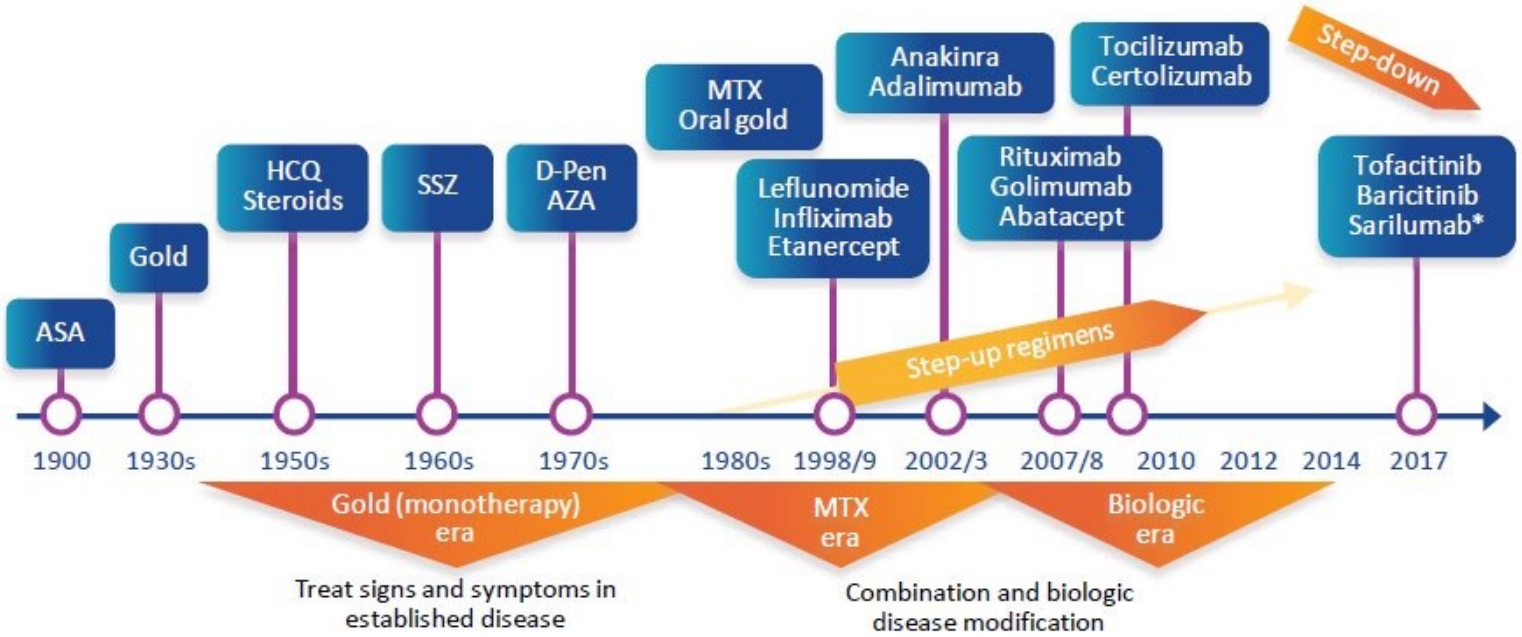
1. Proteine con peso molecolare >1kDa progettate per essere strutturalmente simili alla proteine autologhe
2. Prodotti con tecnica di genetica moleculare e purificati da cellule geneticamente modificate
3. Possono essere modificati ma non metabolizzati

I Biologici

1. Hanno rivoluzionato il trattamento di un ampia varietà di malattia
2. Insulina nel 1982 è la prima proteina terapeutica ricombinante commercializzata
3. Settore in piu rapida crescita nell'industria farmaceutica con un valore stimato attorno $ 150B

Evolution of RA treatments:

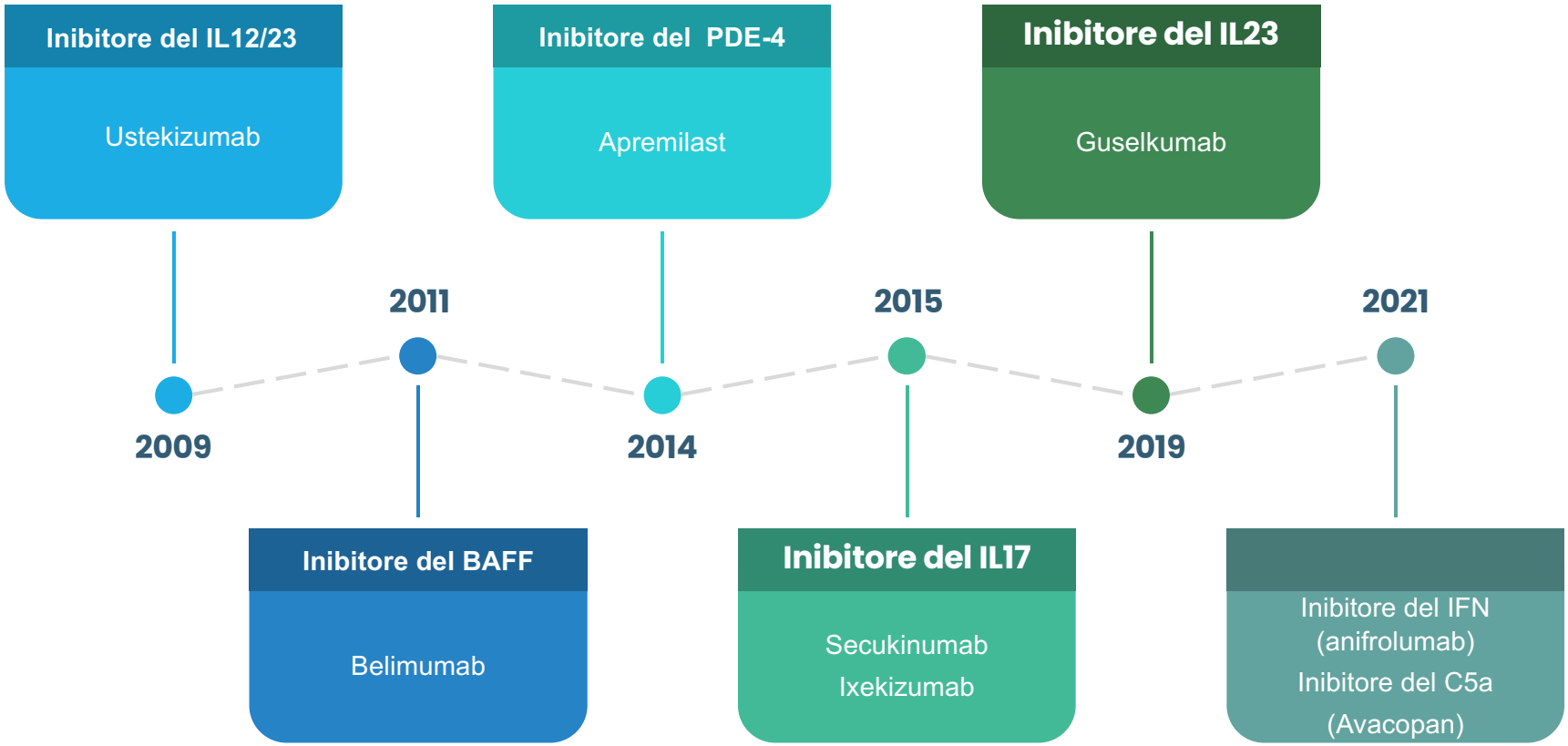
A remarkable story of success?



*Sarilumab is not approved for rheumatoid arthritis in Australia
ADA, adalimumab; ASA, aspirin; AZA, azathioprine; bDMARD, biologic disease-modifying antirheumatic drug;

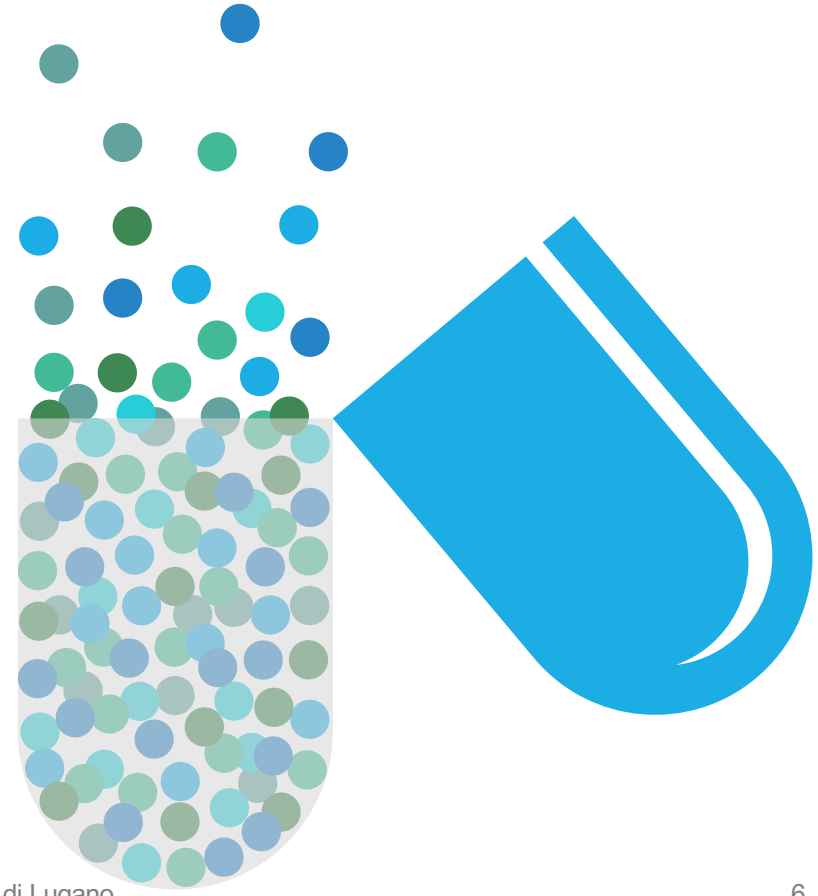
1. Smolen JS, et al. Ann Rheum Dis 2010;69:631–7;
2. Smolen JS, et al. Ann Rheum Dis 2016;75:3–15;
3. Smolen JS, et al. Ann Rheum Dis 2017;0:1–18;
4. Singh JA, et al. Arthritis Care Res 2016;68:1–25;

Evoluzione della terapia biologica in reumatologia



Biologici in Reumatologia: Sicurezza

- Immunogenicità e anticorpi neutralizzanti
- Rischio di eventi avversi
- Rischio di malattia tumorale
- Sicurezza durante la Gravidanza
- Risposta immunitaria alla vaccinazione



Fattori con impatto su Farmacocinetica e immunogeniticità dei biologici

Farmacocinetica	PRODUCT 01
Biologico	• Tipo(Mab o ricettori solubili) • Struttura e dimensione • Isotipo e capacità di legare a FcRn
Catabolismo	• Proteasi
Target (Antigene)	• Solubile o legato alla cellule • Antigen sink
Anti-drug antibodies (ADA)	• Formazione di immuno-complessi • Elimiinazione tramite FcγR
Fattori dei Pazienti	• Peso • Tasso sierico di albumina • Tipo e attività della malattia • Genetica (polimorfismo FcRn e allotipo di immunoglobuline

Immunogenicità	PRODUCT 01
Molecula del biologico	• Sequenza (murina o umano) • Allotipo • Struttura (glicosilazione e altri modifiche post-translazionale • Formulazione
Prodotto	• Dose • Modo e frequenza di Somministrazione • Impurità e aggregati
Target	• Solubile o legato alla cellule
Fattori dei Pazienti	• Tipo e attività della malattia • Altre terapie associate • Genetica

Strand, V et al, Nature Rev. Rheumatology February 2021;17:81-97

Nomenclature of biologic agents

Prefix

Target

- li (lymphocytes or immune system)
- tu/ta (tumor)
- ki (interleukin)
- vi (virus)
- ci (cardiovascular system)

Source

- mo (mouse)
- xi (chimer)
- zu (humanized)
- u (fully human)

Stem

- Mab (monoclonal antibody)
- cept (receptor)
- inib (receptor antagonist)

Rischio di Immunogenicità

Frequenza di anticorpi contro il biologico

Table 1 | **Frequency of anti-drug antibody formation in rheumatic diseases**

Biologic agent or biosimilar	RA	PsA	JIA	AS	Psoriasis	Range	Refs
Abatacept	2–20% (7)	ND	2–11% (2)	ND	ND	2–20% (9)	4
Adalimumab	0–51% (33)	0–54% (8)	6–33% (6)	8–39% (9)	0–51% (12)	0–54% (84)	4
Adalimumab biosimilar (5)[a]	31.8–43.2% (4)	ND	ND	ND	36.8–55.2% (2)	31.8–55.2% (6)	6
Certolizumab pegol	2.8–37% (7)	ND	ND	ND	21% (1)	3–37% (14)	4
Etanercept	0–13% (25)	0% (3)	0–6 % (2)	0 (4)	2–5% (5)	0–13% (37)	4
Etanercept biosimilars (2)[a]	0.3% (1)	ND	ND	ND	0% (1)	0–0.3% (2)	6
Golimumab	2–10% (11)	6% (1)	ND	0–6.4% (2)	ND	0–19% (22)	4
Infliximab[b]	8–62% (48)	15–33% (3)	26–42% (2)	6.1–69% (10)	0–41% (12)	0–83% (114)	4
Infliximab biosimilars (3)[a,b]	48.2–53.0% (3)	ND	ND	25.0% (1)	ND	22.9–53.0% (6)	6
Ixekizumab	ND	5.2–10.3% (2) with methotrexate; 8.6–12.0% (2) as monotherapy	ND	ND	ND	5.2–12.0% (2)	111
Rituximab[b]	0–21% (8)	ND	ND	ND	ND	0–21% (8)	4
Rituximab biosimilars (3)[a,b]	10.0–17.6% (5)	ND	ND	ND	ND	10.0–17.6% (5)	6
Secukinumab	ND	0–0.35% (6)	ND	0–0.69% (6)	0–1% (8)	0–1% (14)	4,108
Tocilizumab	0–16% (14)	ND	1–8% (3)	ND	ND	0–16% (17)	4
Ustekinumab	ND	8–11% (3)	ND	ND	4–8.6% (10)	1–11% (15)	4

The numbers in this table refer to percentages of patients with anti-drug antibodies across various randomized controlled trials, with the number of trials in parentheses. Adapted from REF.[4], Springer Nature Limited. AS, ankylosing spondylitis; JIA, juvenile idiopathic arthritis; ND, no data; PsA, psoriatic arthritis; RA, rheumatoid arthritis. [a]Refers to the number of biosimilars for a particular biologic agent. [b]All patients in these trials were receiving background methotrexate therapy.

Strand, V et al, Nature Rev. Rheumatology February 2021;17:81-97

Table 3. Comparison between the prevalence ranges for ADAs to various biologic agents in adult *versus* paediatric populations.

Prevalence of ADAs	Adults with inflammatory arthritis (%)	Children with juvenile idiopathic arthritis (%)
TNF-α blockers		
Adalimumab and biosimilars	0–67	6–45
Infliximab and biosimilars	6.1–62	26–37
Etanercept and biosimilars	0–13	0–33
Golimumab	2–39.9	46.8
Certolizumab	2.8–65	Data not available
B-cell depletion		
Rituximab and biosimilars	0–21	Data not available
Co-stimulatory blockade		
Abatacept IV	2–20	2–11
Abatacept SC	2–20	2–11
IL-6 blockade		
Tocilizumab	0–16	1–8
Sarilumab	7–24.6	Data not available
IL-17 blockade		
Sekukinumab	0–1	Data not available
Ixekizumab	5.3–9	Data not available
IL-12/23 blockade		
Ustekinumab	5.7–11	Data not available
IL-1 blockade		
Anakinra	50.1–70.9	81.8
Canakinumab	Data not available	3.1–8
Rinolacept	Data not available	54.2

ADA, anti-drug antibody; IL, interleukin; IV, intravenous; SC, subcutaneous; SD, standard deviation; TNF, tumour necrosis factor.

Parikh, CR. Et al, Ther Adv Musculoskel Dis 2021, Vol. 13: 1–27

Frequenza di anticorpi contro I biologici

Table 2 - Monoclonal antibodies approved for the treatment of psoriasis and psoriatic arthritis, and the anti-drug antibodies (ADAs) rates reported for them (1,34).

mcAB	Target Molecule	Format	Indication	%ADA	%ADA neut
ADL	TNF-α	IgG1 human	RA, PsO	28%, 6–45%	no report
BDL	IL-17R	IgG2 human	Plaque PsO	2.7%	0%
GLM	TNF-α	IgG1 human	RA and PsA	31.7%	no report
GSK	IL-23 p19	IgG1 human	PsO placa	5.5%	0.4%
IFX	TNF	IgG1 chimeric	CD	66.7% cumulative in RA 5.4–43.6% PsO	no report
IXK	IL-17a	IgG4 humanized	PsO	9%	no report
RSK	IL-23 p19	IgG1 humanized	Plaque PsO	24%	14%
SCK	IL-17a	IgG1 human	PsO	0.41%	0.2%
TDK	IL-23 p19	IgG1 humanized	Plaque PsO	4.1–8.8%	0.6–3.34%
UTK	IL-12/23	IgG1 human	PsO	6.5%	no report

Abbreviations: ADA neut: neutralizing anti-drugs Antibodies; mcAB: Monoclonal antibody; ADL: Adalimumab; BDL: Brodalumab; GLM: Golimumab; GSK: Guselkumab; IFX: Infliximab; IXK: Ixekizumab; RSK: Risankizumab; SCK: Secukinumab; TDK: Tildrankizumab; UTK: Ustekizumab.

Flores, R. et al, Clinics 2021

Conseguenza dell'Immunogenicità

1. **Lo sviluppo di anticorpi contro il biologico**
   - Perdità di efficacia
2. **Provocare degli eventi avversi**
   - Reazione d'infusion
   - Ipersensibilità ritardata
   - Anafilassi
3. **Eliminazione accelerata**

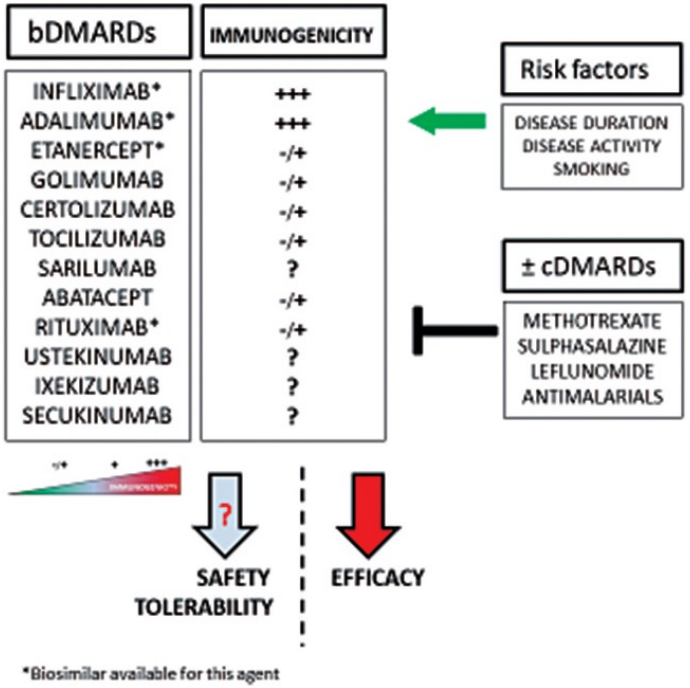


Fig. 1. Biological disease-modifying anti-rheumatic drugs (bDMARDs) are associated with immunogenicity, leading to the development of anti-drug antibodies that affect drug efficacy and may affect drug safety and tolerability. The development of anti-drug antibodies seems to be influenced by multiple risk factors and may be modulated by the concomitant use of conventional synthetic DMARDs (cs-DMARDs).

Benucci, M et al, Annals of laboratory medicine 2020

Tasso di ritenzione dei biologici

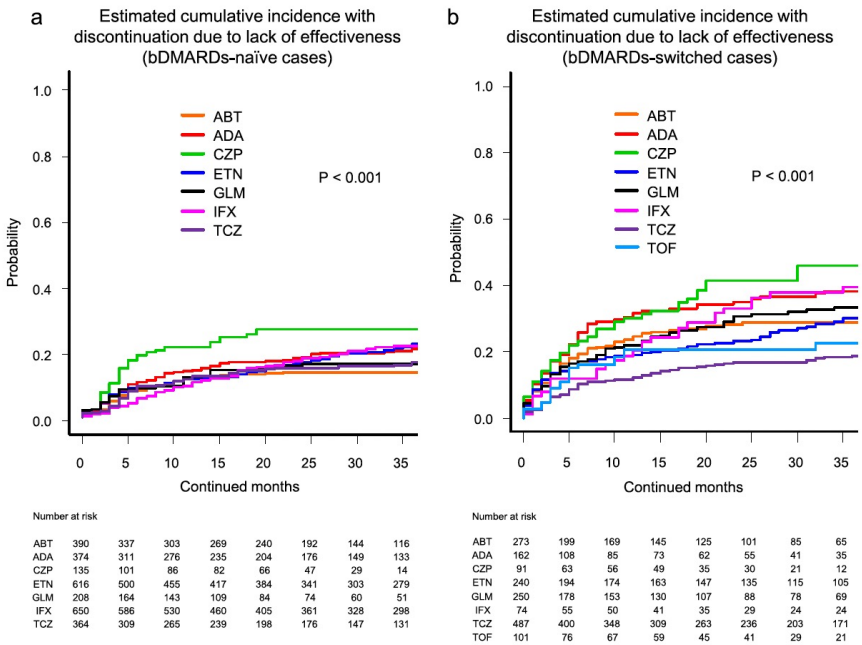


Fig. 1 Estimated cumulative incidence with discontinuation due to lack of effectiveness in the bDMARDs-naïve cases (**a**) and the bDMARDs-switched cases (**b**). ABT abatacept, ADA adalimumab, CZP certolizumab pegol, ETN etanercept, GLM golimumab, IFX infliximab, TCZ tocilizumab, TOF tofacitinib, bDMARDs biological disease-modifying antirheumatic drugs

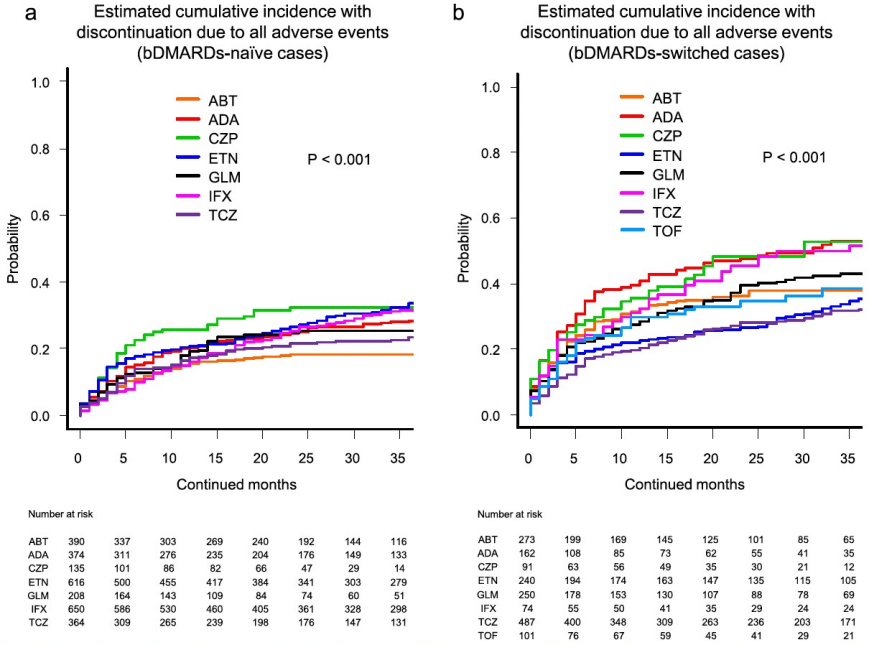


Fig. 4 Estimated cumulative incidence with discontinuation due to all adverse events (including lack of effectiveness and toxic adverse events) in the bDMARDs-naïve cases (**a**) and the bDMARDs-switched cases (**b**). ABT abatacept, ADA adalimumab, CZP certolizumab pegol, ETN etanercept, GLM golimumab, IFX infliximab, TCZ tocilizumab, TOF tofacitinib, bDMARDs biological disease-modifying antirheumatic drugs

Ebina, K. et al, Arthritis Research and Therapy 2020

Table 3 Hazard ratio of treatment discontinuation in the bDMARDs-naïve cases (Fine-Gray hazard competing risk regression model, adjusted by baseline age, sex, disease duration, concomitant PSL and MTX usage, and starting date of bDMARDs)

Variable	Reference	HR (95% CI)						
	ABT ($n = 390$)	ADA ($n = 374$)	CZP ($n = 135$)	ETN ($n = 616$)	GLM ($n = 208$)	IFX ($n = 650$)	TCZ ($n = 364$)	*P* value
Lack of effectiveness	1	1.4 (1.0–2.1)	2.4 (1.5–3.8)***	1.7 (1.2–2.4)**	1.1 (0.7–1.7)	1.5 (1.1–2.2)*	1.1 (0.8–1.7)	< 0.001
All toxic adverse events	1	2.8 (1.5–5.2)***	1.7 (0.7–4.0)	4.0 (2.3–6.9)***	2.5 (1.3–4.8)**	4.3 (2.5–7.3)***	2.2 (1.2–4.2)*	< 0.001
Non-toxic reasons	1	0.8 (0.5–1.3)	0.3 (0.1–0.9)*	1.1 (0.7–1.6)	1.5 (0.9–2.5)	1.0 (0.7–1.5)	1.1 (0.7–1.8)	0.07
Remission	1	2.9 (1.5–5.4)***	1.8 (0.8–4.4)	1.0 (0.5–2.0)	2.4 (1.2–5.0)*	3.1 (1.7–5.6)***	2.5 (1.3–4.8) **	< 0.001
All adverse events (including lack of effectiveness and toxic adverse events)	1	1.8 (1.3–2.5)***	2.5 (1.6–3.7) ***	2.3 (1.7–3.1)***	1.5 (1.0–2.2)*	2.1 (1.6–2.9)***	1.4 (1.0–2.0)*	< 0.001

bDMARDs biological disease-modifying antirheumatic drugs, *PSL* prednisolone, *MTX* methotrexate, *HR* hazard ratio, *95% CI* 95% confidence interval, *ABT* abatacept, *ADA* adalimumab, *CZP* certolizumab pegol, *ETN* etanercept, *GLM* golimumab, *IFX* infliximab, *TCZ* tocilizumab
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Ebina, K. et al, Arthritis Research and Therapy 2020

Table 4 Hazard ratio of treatment discontinuation in the bDMARDs-switched cases (Fine-Gray hazard competing risk regression model, adjusted by baseline age, sex, disease duration, concomitant PSL and MTX usage, starting date, and number of switched bDMARDs)

	Reference	HR (95% CI)							
Variable	ABT ($n = 273$)	ADA ($n = 162$)	CZP ($n = 91$)	ETN ($n = 240$)	GLM ($n = 250$)	IFX ($n = 74$)	TCZ ($n = 487$)	TOF ($n = 101$)	*P* value
Lack of effectiveness	1	1.3 (0.9–1.8)	1.5 (1.0–2.2)*	1.1 (0.8–1.5)	1.0 (0.7–1.3)	1.3 (0.9–2.0)	0.6 (0.4–0.8)***	0.8 (0.5–1.2)	< 0.001
All toxic adverse events	1	1.8 (1.0–3.1)	0.8 (0.3–2.0)	0.4 (0.2–0.9)*	1.0 (0.6–1.9)	1.2 (0.5–2.7)	1.4 (0.9–2.3)	1.8 (0.9–3.5)	0.004
Non-toxic reasons	1	1.2 (0.6–2.2)	0.3 (0.1–1.1)	0.8 (0.4–1.4)	0.8 (0.4–1.5)	0.9 (0.4–2.4)	0.8 (0.5–1.3)	0.6 (0.2–1.5)	0.5
Remission	1	0.8 (0.1–5.0)	0.9 (0.1–9.2)	1.4 (0.3–6.1)	1.8 (0.4–7.7)	1.9 (0.4–10.7)	1.5 (0.4–5.4)	2.3 (0.4–13.8)	0.9
All adverse events (including lack of effectiveness and toxic adverse events)	1	2.7 (1.6–4.3)***	2.2 (1.4–3.4)**	1.2 (0.8–2.0)	1.4 (1.0–2.1)	2.0 (1.0–3.7)*	0.9 (0.6–1.4)	1.1 (0.6–1.9)	< 0.001

bDMARDs biological disease-modifying antirheumatic drugs, *PSL* prednisolone, *MTX* methotrexate, *HR* hazard ratio, *95% CI* 95% confidence interval, *ABT* abatacept, *ADA* adalimumab, *CZP* certolizumab pegol, *ETN* etanercept, *GLM* golimumab, *IFX* infliximab, *TCZ* tocilizumab, *TOF* tofacitinib
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Ebina, K. et al, Arthritis Research and Therapy 2020

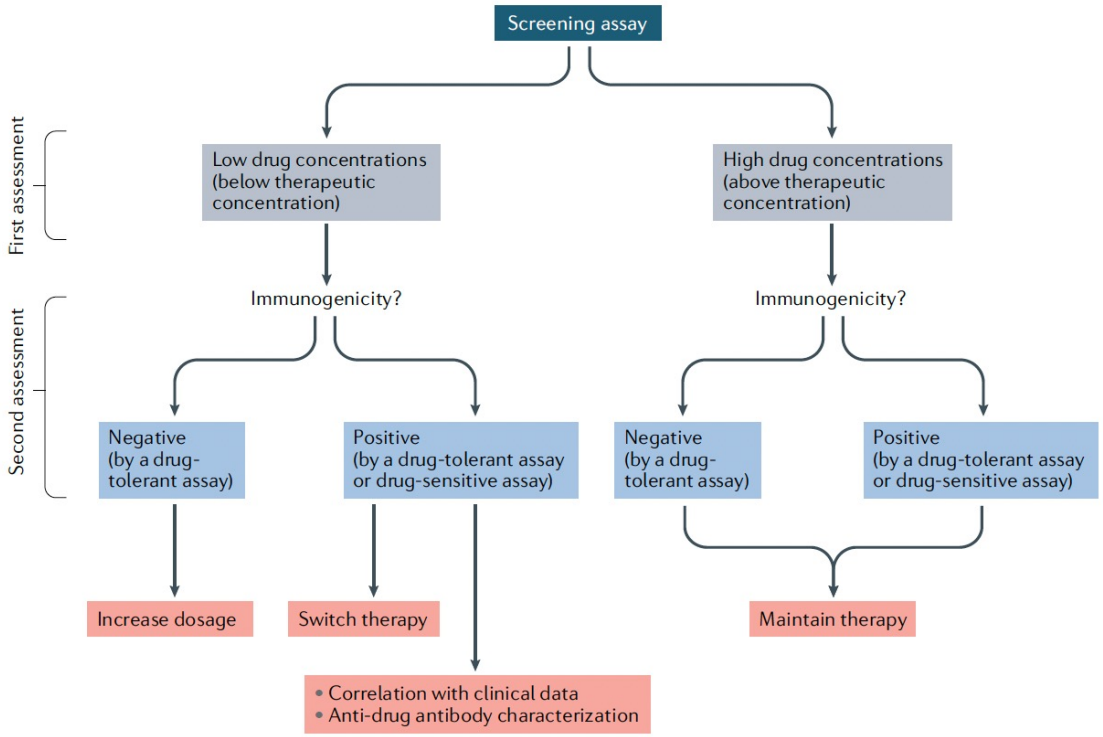
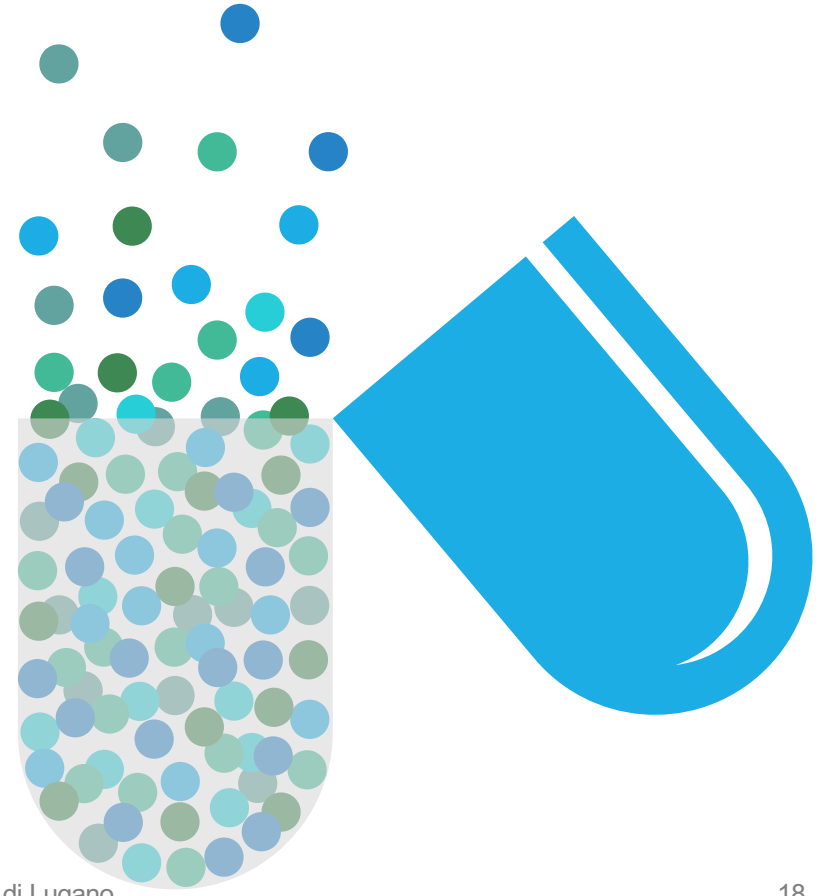


Fig. 4 | **Therapeutic drug monitoring strategies.** A potential therapeutic drug monitoring decision algorithm that integrates information regarding serum drug concentrations and immunogenic responses and that could be used in the assessment of patients with rheumatoid arthritis being treated with TNF inhibitors. The algorithm also illustrates how the assays can potentially help to guide treatment strategy. For example, if loss of efficacy of an anti-TNF monoclonal antibody is associated with the development of anti-drug antibodies, then a different TNF inhibitor might be effective. However, if loss of efficacy is not associated with anti-drug antibody development, then the best strategy might be to switch to a different therapeutic class.

Strand, V et al, Nature Rev. Rheumatology February 2021;17:81-97

Biologici in Reumatologia: Sicurezza

- Rischio di eventi avversi
- Rischio di malattia tumorale
- Sicurezza durante la Gravidanza
- Risposta Immunitaria alla vaccinazione



Classificazione:

Tempo di insorgenza

- Immediata (<1h dalla somministrazione)
- Ritardata (da 1h- 1 settimana dopo la somministrazione)

Meccanismo

- Allergico (IgE-mediated)
- Non-Allergico

Sekerel,BE et al, Curr Treat Options Allergy 2020

Classificazione: Reazioni avverse ai biologici

Table 2
Proposed classification of adverse reactions to biologic agents

Type	Example Reaction (Causative Medication)
α: Overstimulation	Cytokine release syndrome (cytokine storm) (muromunab, TGN1412)
β: Hypersensitivity	Common acute infusion reactions (rituximab), delayed infusion reactions (etanercept, adalimumab), anaphylaxis (muromunab, cetuximab, omalizumab)
γ: Cytokine or immune imbalance	
Immunodeficiency	Increased risk of tuberculosis (anti-TNF agents) Hypogammaglobulinemia (rituximab)
Autoimmunity	Systemic lupus erythematosus or vasculitis (IFN-γ)
Atopic disorders	Atopic dermatitis (anti-TNF agents)
δ: Cross-reactivity	Acne from anti-EGFR (cetuximab)
ε: Nonimmunologic side effects	Neuropsychiatric side effects including confusion or depression (IFN-α)

Modified from Pichler WJ. Adverse side-effects to biological agents. Allergy 2006;61(8):917; with permission.

Patel, S et al, K. et al, Immunol Allergy Clin N. Am 2017

Eventi Avversi

Biologici	Infezione	Altri
Inibitore del TNF-alfa	Tuberculosi	Psoriasi paradossale, Lupus like disease
Anti-IL6		Perforazione intestinale (FR:diverticolosi /diverticolite ; GC)
Anti-IL17	Candidosi	IBD
Abatacept		
Rituximab	Pneumocystis jiroveci	
Inibitore del chinase JAK	Herpes Zoster	TVP e embolia polmonare

Sepriano, A. et al, Ann Rheum Dis 2020
Collamer, AN et al, Arthritis Rheum 2008
Mease, P et al, Ann. Rheum Dis, 2020

Tada, Y et al, Int. J. of Molecular Sciences 2021
Gordon, KB et al, NEJM 2016
Blauvelt, A et al, Exp Opin Drug Saf 2016

Van der Kerhof, PC et al., J. Am Acad Derm 2016
Huber, W et al, Gut 2012

Eventi Avversi: Reazione d'infusione

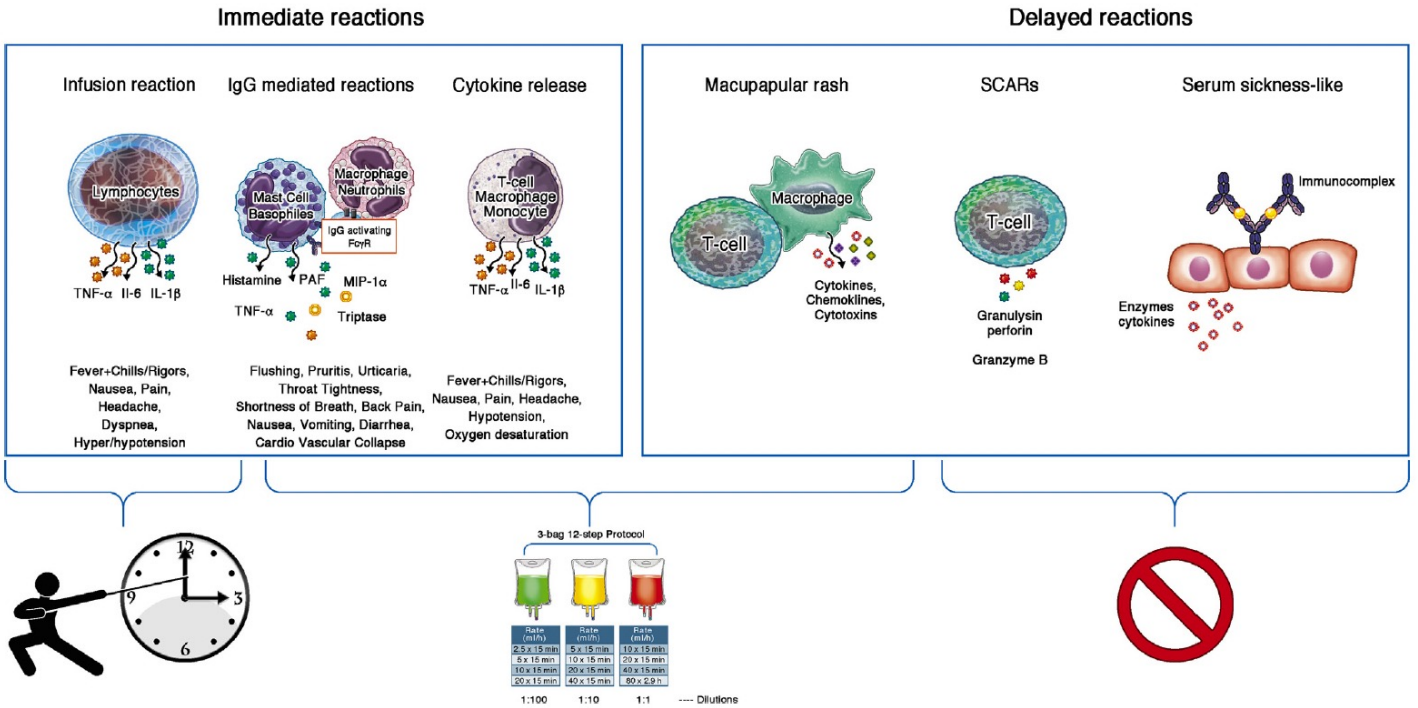


FIG 1. Diagram outlining the proposed classification based on the underlying mechanisms, potential mediators, and management recommendations for non-IgE adverse reactions to biologics.[1]

Castells, M, J. of Allergology Clin. Immunology 2021

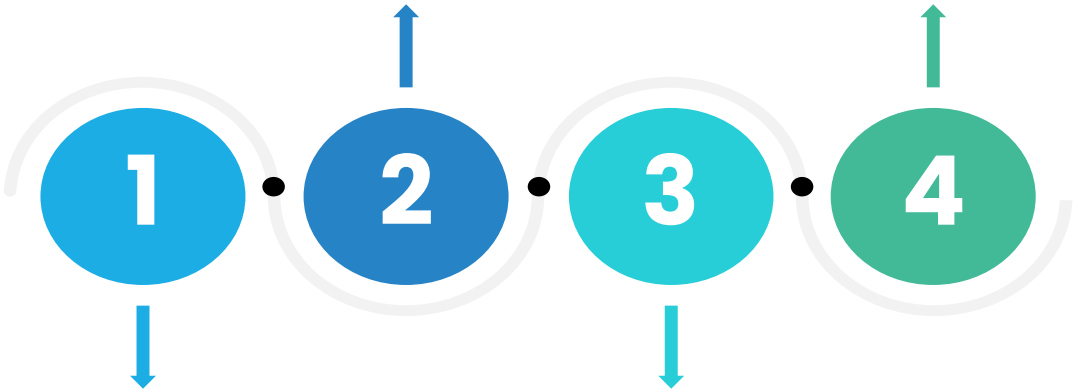
Trattamento e Prevenzione di Reazione d'infusion

Riprendere la somministrazione

- Solo in casi leggeri: rallentare la somministrazione

Prevenzione a lungo termine

- Co-medicazione con immunosuppressive (MTX ecc.)



Sospendere l'infusione

- In casi leggeri: 1g Paracetamolo e anti-istaminico
- In casi gravi con anafilassi: Epinefrine/adrenalina IM con anti-istaminico IV e Metilprednisone IV

Somministrazione successivi

- In casi leggeri: pre-medicazione (paracetamolo, anti-istaminico e cortisone
- In casi gravi: cambiare biologico oin caso di mancanza di alternative: protocollo di desensibilizzazione

Spertini, M et al, Nat. Rev. Rheumatology 2014

Algoritmo nella gestione di reazione d'ipersensibilità

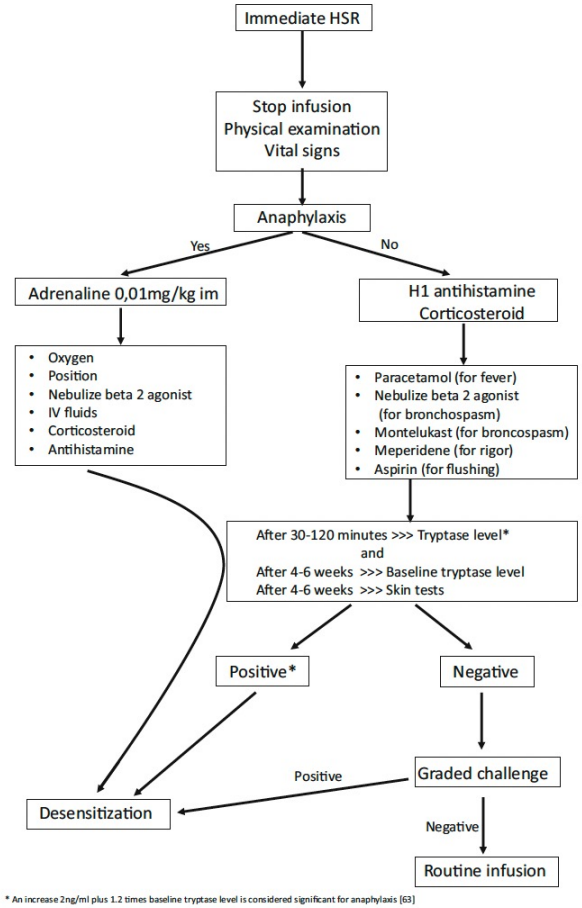
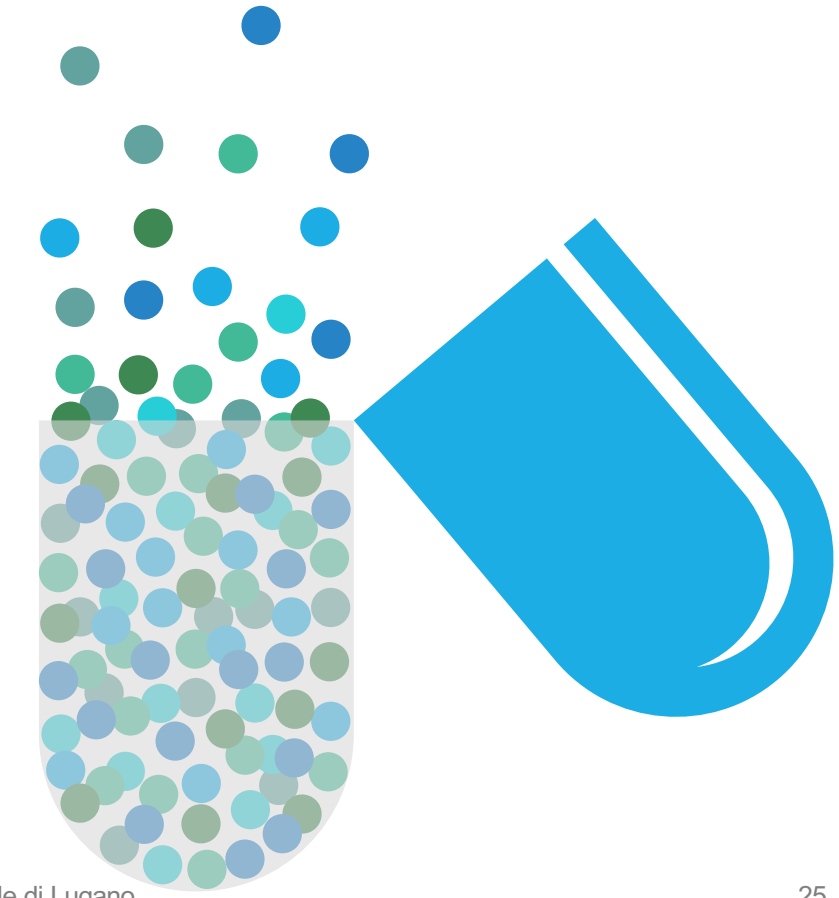


Fig. 1. The algorithm for management of hypersensitivity reactions with biologics.

Sekerel, BE et al, Curr. Treat Options Allergy 2020

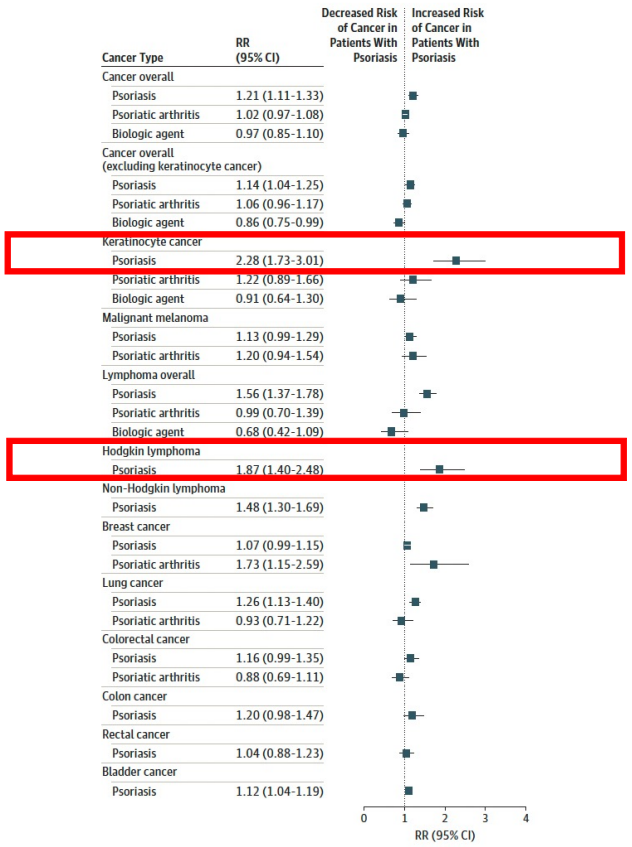
Biologici in Reumatologia: Sicurezza

- Rischio di malattia tumorale
- Sicurezza durante la Gravidanza
- Risposta Immunitaria alla vaccinazione



Rischio di malattia tumorale

Figure 2. Risk Ratios (RRs) for Cancers



Risk ratios for cancers in patients with psoriasis and psoriatic arthritis, and in patients with psoriasis treated with biologic agents compared with conventional therapy.

Table 3 Observed number (Obs) of deaths and overall mortality in patients with rheumatoid arthritis with cancer according to bDMARD treatment

	All n=1678			Extent of disease recorded n=1326			
Treatment	Deaths Obs	Person-years	Adjusted* HR (95% CI)	Deaths Obs	Person-years	Adjusted* HR (95% CI)	Further adjusted† HR (95% CI)
Non-user of bDMARDs	207	2461	1 (Ref)	150	2022	1 (Ref)	1 (Ref)
Ever bDMARDs	135	1225	1.25 (0.99 to 1.57)	110	982	1.35 (1.04 to 1.76)	1.23 (0.94 to 1.60)
bDMARDs before first cancer	93	272	1.50 (1.15 to 1.97)	75	214	1.53 (1.13 to 2.09)	1.20 (0.88 to 1.63)
bDMARDs after first cancer	42	953	0.92 (0.64 to 1.31)	35	767	1.08 (0.73 to 1.61)	1.29 (0.86 to 1.94)
bDMARDs only after first cancer	23	760	1.01 (0.62 to 1.65)	20	640	1.19 (0.69 to 2.04)	1.36 (0.78 to 2.39)
bDMARDs both before and after first cancer	19	193	0.85 (0.52 to 1.38)	15	128	0.99 (0.57 to 1.73)	1.22 (0.70 to 2.13)
Type of bDMARD after first cancer‡							
TNF-I	35	723	0.96 (0.66 to 1.41)	29	568	1.13 (0.73 to 1.74)	1.42 (0.91 to 2.20)
Rituximab	9	235	0.86 (0.43 to 1.72)	8	205	1.13 (0.54 to 2.40)	1.11 (0.53 to 2.35)

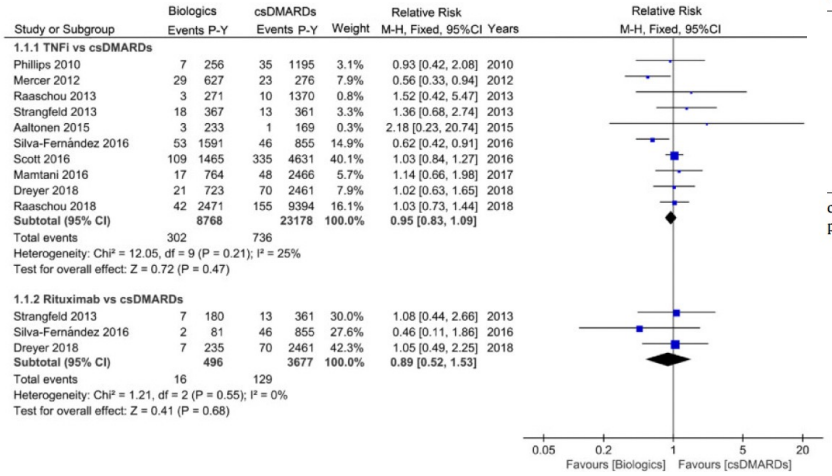
*Adjusted for age, gender, calendar time, cancer site.
†Further adjusted for extent of disease.
‡If a patient is treated with both TNF-I and rituximab after first cancer, the patient will contribute person-years to both types of bDMARD.
bDMARD, biological disease-modifying antirheumatic drug; TNF-I, tumour necrosis factor-alpha inhibitor.

Dreer, L. et al, Ann Rheum Dis. 2018
Vaengebjerg, S et al, JAMA Dermatology 2020

Rischio di malattia tumorale

Rischio di ricaduta o nuovi tumori

FIG. 2 Relative risk of cancer recurrence between biologic and csDMARDs



TNFi: TNF inhibitor; csDMARDs: conventional synthetic DMARDs.

Rischio di tumori sotto terapia

Table 2
Range of Incidence rates of overall malignancy and specific cancers.

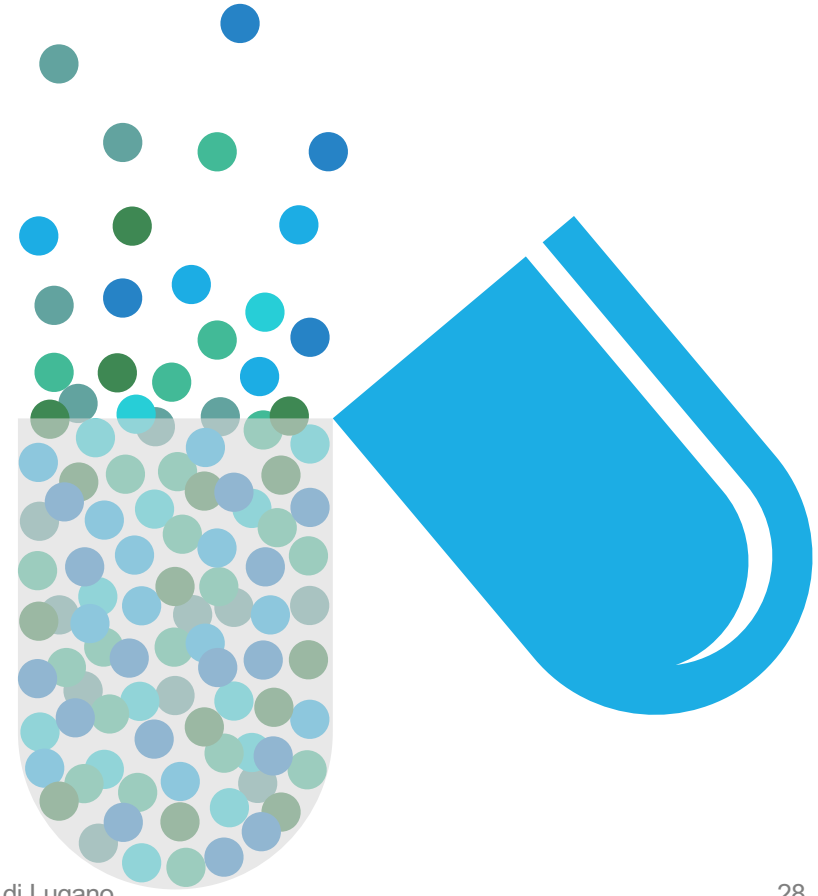
	Number of patients (pys of exposure)	Range of Incidence rates (per 1000 patient-years)				
		Overall malignancy	Solid cancer	Hematological cancer	NMSC	Melanoma
csDMARDs	122,834 (581,118)	8.60–18.68	3.84–11.75	0.69–11.78	1.71–7.10	0–0.86
TNFi	166,073 (481,654)	4.46–21.46	1.94–10.19	0.19–10.71	1.04–14.6	0.19–1.36
Rituximab	13,662 (44,576)	8.10–10.74	4.05–9.85	0–1.14	1.59–4.05	0.45–0.60
Tocilizumab	>17,506 (>20,622)	7.40–23.18	4.78–10.48	0.54–1.62	0–0.9	0.54–1.09
Abatacept	9419 (22,424)	7.60–47.58	5.09–9.80	0–2.40	2.26–21.2	0–1.10
Tofacitinib	2221(>4506)	8.92–22.76	11.38	0	10.93	NA

csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; TNFi: tumor necrosis factor inhibitors; NMSC: non-melanoma skin cancer. pys: patient-years.

Xie, W et al, Seminars in Arthritis and Rheumatism 2020
Xie, W. et al Rheumatology 2020

Biologici in Reumatologia: Sicurezza

- Sicurezza durante la Gravidanza
- Risposta Immunitaria alla vaccinazione



Biologici durante la gravidanza e allattamento

Biologici	Pre-concezione	Gravidanza	Allattamento
Inibitore del TNF-alfa (Certolizumab)	✓✓	✓✓	✓✓
Altri inibitori del TNF-alfa	✓	✓ 1° e 2° tri	✓✓
Rituximab	✓ Fino a concezione	✓ Solo in caso di urgenza	✓✓
Inibitore IL-1;IL-6; IL-17	✓ Fino a concezione	✗	✓✓
Belimumab	✓ Fino a concezione	✗	✓
Abatacept	✓ Fino a concezione	✗	✓

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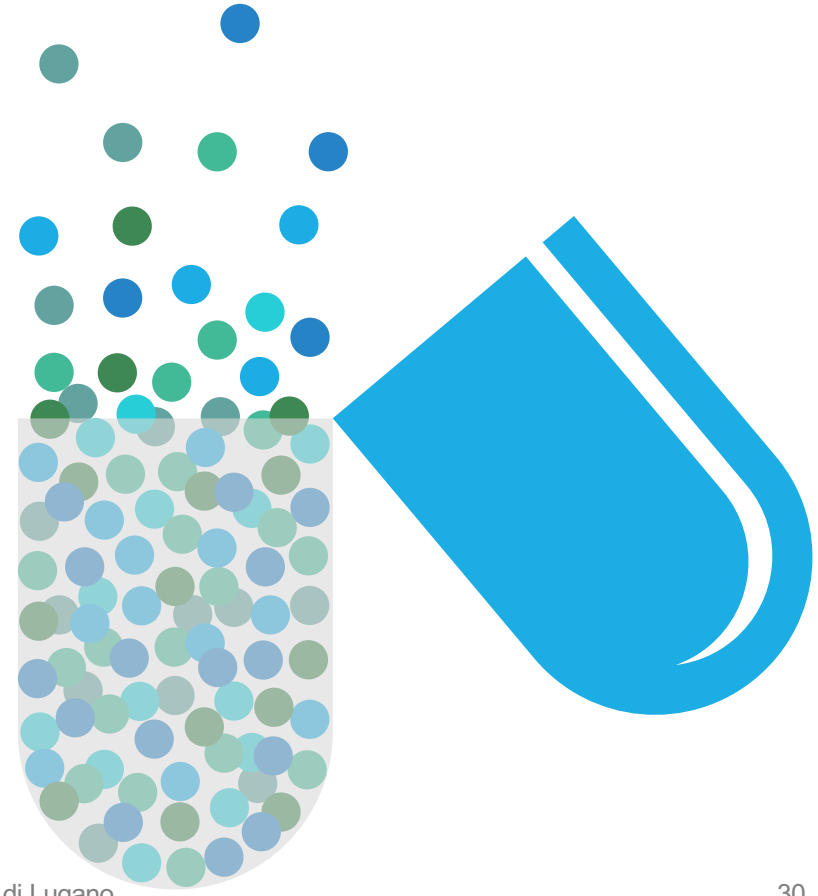
Biologici in Reumatologia: Sicurezza



- **Risposta immunitaria alla vaccinazione**

Immune Response to Vaccine

Biologicals	Influenza	Tetanus	Hepatitis B
Anti-TNF	Good (reduced with MTX+ TNFi)		Reduced
Anti-IL6	Good	Good	
Abatacept	Reduced	Reduced	
Rituximab	Reduced to blunted	Reduced with MTX	
Other DMARDs	Good (AZA with negative effect)	Reduced	Moderate
Glucocorticosteroides	Good	Good	Moderate

Buehler, S et al. Swiss medical weekly 2015

Immune Response to Vaccine

Biologicals	Hepatitis A	Pneumococcus PPV	Pneumococcus PCV
Anti-TNF	Good	Moderate-Good	Good
Anti-IL6	Good	Good	
Abatacept		Reduced	Severely Reduced
Rituximab		Reduced	Severely Reduced
Other DMARDs	Good	Moderate-Good	Reduced
Glucocorticosteroides	Good	Moderate-Good	Good

Buehler, S et al. Swiss medical weekly 2015

Immune Response to Vaccine

Biologicals	Haemophilus	HPV	Tetanus/diptheria /pertussis/polio
Anti-TNF			
Anti-IL6			
Abatacept			
Rituximab			
Other DMARDs	Good (Reduced for CYC and AZA)	Good (negative effect of MMF)	
Glucocorticosteroides	Good	Good	

Buehler, S et al. Swiss medical weekly 2015

Vaccini con virus attenuate o vivi

Terapia	HZV
Prednisone <20mg/die Sulfasalazine Hydroxychlorochine	✓
MTX <0.4mg/kg/settimana	✓
AZA <3mg/kg/die 6-Mercaptopurine <1.5mg/kg/die	✓
MMF, CYC, Leflunomide Ciclosporina e Tacrolimus	✗
Inibitore TNF-alfa, IL6, IL12/23; RTX, Abatacept	✗

Terapia	MMF/Febbre Gialla
Prednisone<20mg/die Sulfasalazine Hydroxychlorochine	✓
MTX <0.4mg/kg/settimana	✓
AZA 6-Mercaptopurine	✗
MMF, CYC, Leflunomide Ciclosporina e Tacrolimus	✗
Inibitore TNF-alfa, IL6, IL12/23; RTX, Abatacept	✗

Buehler, S et al. Swiss medical weekly 2015

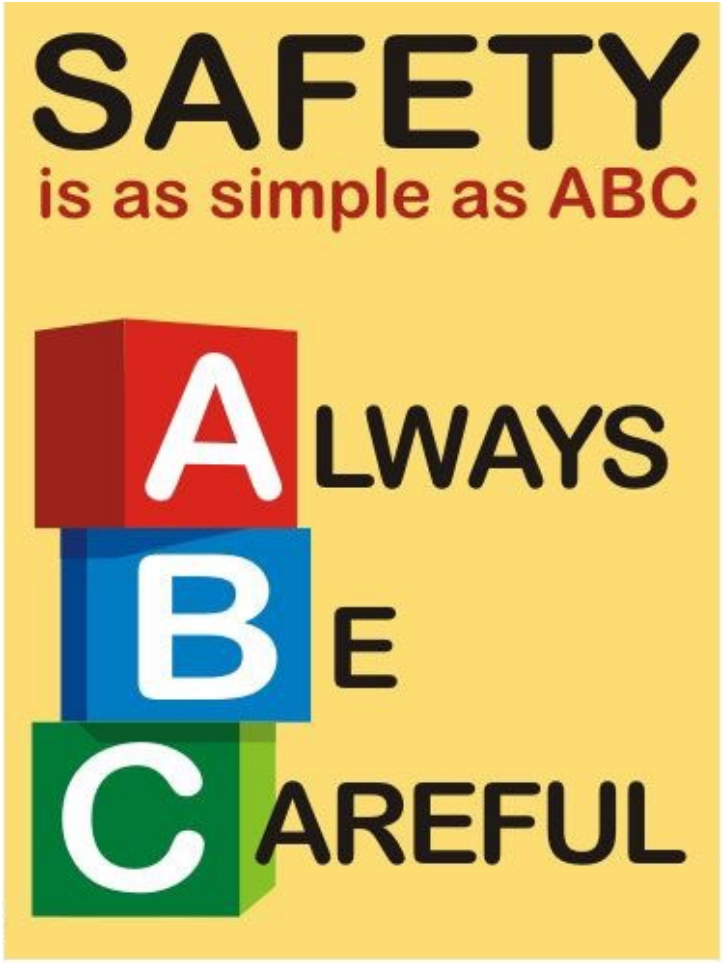
Vaccinazione con virus vivi o attenuati

Terapia	MMR, HZV, Febbre gialla
Prednisone >20mg/die	1 mese dopo la sospensione
Etanercept	1 mese dopo la sospensione
Methotrexate(>20mg/sett) Leflunomide	1-3 mesi dopo la sospensione Almeno 2 anni dopo la sospensione
Inibitore TNF; IL6; IL 12/23 Abatacept	3 mesi dopo la sospensione
Rituximab	Almeno 12 mesi dopo la sospensione

Buehler, S. et al Swiss medical weekly 2015

Take Home Message

- L'immunogenicità dei biologici induce lo sviluppo di anticorpi contro loro
  - provoca la perdità di efficacia del biologico
  - causa eventi avversi
- Non aumento del rischio di sviluppo di malattia tumorale con le terapie biologiche
- Uso in gravidanz considerata sicura per gli inibitori del TNF-alfa
- Vaccinazione importante nella cura generale dei nostri pazienti sotto le terapie biologiche


SAFETY
is as simple as ABC
ALWAYS
BE
CAREFUL