Confronto del pattern d'uso e delle caratteristiche degli utilizzatori di farmaci biologici approvati per le malattie infiammatorie croniche immuno-mediate nei trial clinici registrativi vs. real-world setting: uno studio multiregionale dal Progetto VALORE

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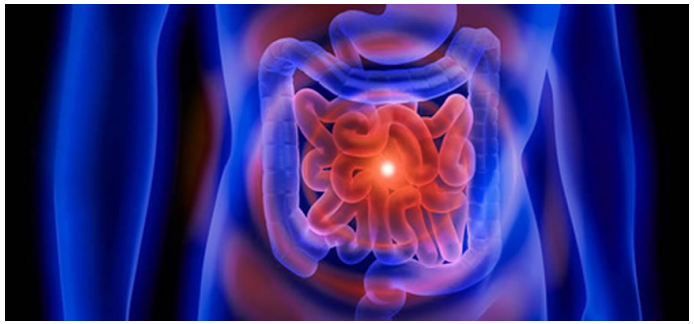
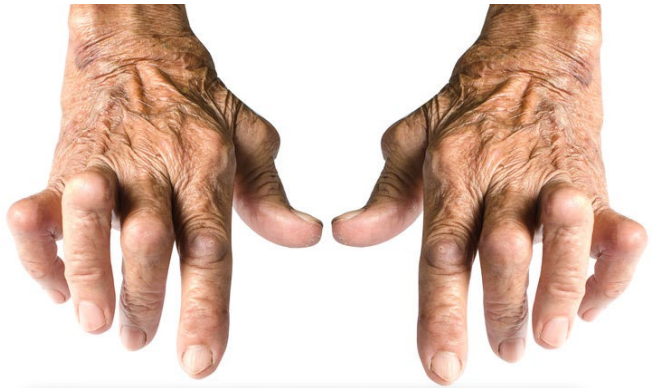
Presentazione del Rapporto Farmaci in Toscana 2022

ARS TOSCANA agenzia regionale di sanità
Regione Toscana
SST Servizio Sanitario della Toscana

Prevalence of immune-mediated inflammatory diseases (IMIDs) in Italy



IBD (*Crohn's disease and ulcerative colitis*):
0.4% (*250,000 patients*)



Rheumatoid arthritis : 0.3% (*200,000 patients*)
Spondyloarthritis: 0.1% (*60,000 patients*)

Psoriasis: 2.8% (*1,680,000 patients*)
Psoriatic arthritis: 0.4% (*250,000 patients*)

Biological drugs approved for IMIDs

- **TNF-alfa inhibitors** (*infliximab, etanercept, adalimumab, certolizumab pegolato, golimumab)*
- **Interleukin inhibitors** (*anakinra, tocilizumab, secukinumab, ustekinumab, ixekinumab, brodalumab, sarilumab, guselkumab, tildrakizumab, risankizumab)*
- **Selective immunosuppressants** (*abatacept, vedolizumab)*
- **Monoclonal antibodies** *(rituximab)*

RW patients

RCTs patients

Ideal World

Pre-marketing studies

- Limited number of patients
- Selected patients
- Limited and defined duration
- Excellent compliance (physicians and patients)

Actual world

Daily clinical practice

- Undefined number of patients
- Heterogeneous duration
- Non selected patients
- Co-morbidities
- Polypharmacy
- Compliance?

Aims

- To compare the **demographic characteristics** of **patients** enrolled in **pivotal RCTs of biologics approved for IMIDs** to those of patients treated with biologics **from seven Italian regions in the years 2010-2020**, using the Italian distributed multi-regional database network of the Italian "**VALORE" project**.

- To measure the extent of **biologic users treated in real-world setting** that would **not** have been **eligible** for inclusion into **RCTs**.

Methods - 1

- *Data sources:*
  - **pivotal phase III RCTs of biologics approved for IMIDs up to December 31, 2020**
  - **claims databases** from **7 Italian regions** (*Tuscany, Sicily, Veneto, Apulia, Lazio, FVG, Emilia Romagna*) from **2010 and 2020**;

- *Study population:*
  - RCTs: **IMID patients** (*RA, PsA, PsO, SpA, CD, UC*) treated with **biologics**;
  - RW: **incident** (no previous use) **users of biologics** treated for **IMIDs.**

Coding algorithms were used to separately identify the main indications for use (i.e., RA, PsA, AS, PsO, CD or UC) of biological drugs from regional claims databases.

- *Study drugs:* abatacept, adalimumab, anakinra, brodalumab, certolizumab pegol, etanercept, golimumab, guselkumab, infliximab, ixekizumab, risankizumab,sarilumab, secukinumab, tildrakizumab, tocilizumab, ustekinumab, vedolizumab

Methods - 2

- *Study analyses:*
  - Comparison of the **baseline characteristics of biologic users from pivotal RCTs vs. RW setting**: *sex and mean age;*
  - Proportion of biological drug users in RW setting who would not be **eligible for inclusion into the respective pivotal RCT.**

All the analyses were stratified by individual compound and indication for use.

Phase III, pivotal clinical trials of biologics approved for IMIDs, stratified by indication for use

Biological drug	Indication for use	Clinical trial name (NCT code, if available)	N. of patients randomized to treatment arm	Duration of the double-blind period (weeks)
Abatacept	RA	AIM, (NCT00048568)	433	48
		ATTAIN, or IM101029	258	24
		ASSURE, or IM101031 (NCT00124982)	959	48
	PsA	PsA-II, or ASTRAEA (NCT01860976)	213	24
Adalimumab	RA	ARMADA or DE009	209	24
		DE011	434	26
		DE019 (NCT00195702)	207	52
		STAR or DE031	318	24
	AS	ABILITY-1 (NCT00939003)	91	12
	PsO	REVEAL (NCT00237887)	250	52
		CHAMPION (NCT00235820)	108	16
	PsA	ADEPT	151	24
	CD	CLASSIC I	225	4
		GAIN (NCT00105300)	159	4
		CHARM	517	56
	UC	ULTRA-1 (NCT00385736)	260	8
		ULTRA-2 (NCT00408629)	248	52
Anakinra	RA	960180	345	24
		0560	351	24
		990145	250	52
Brodalumab	PsO	AMAGINE-1 (NCT01708590)	441	52
		AMAGINE-2 (NCT01708603)	1222	52
		AMAGINE-3 (NCT01708629)	1253	52
Certolizumab pegol	RA	RAPID-I (NCT00152386)	783	52
		RAPID-II (NCT00175877)	492	24
	AS	RAPID-axSpA, or AS001	218	24
		(NCT01087762)		
		C-OPTIMISE (NCT02505542)	209	48
		C-axSpAnd, or AS0006 (NCT02552212)	159	52
	PsA	RAPID-PSA, or PSA001 (NCT01087788)	273	24
	PsO	CIMPASI 1 (NCT02326298)	183	48
		CIMPASI 2 (NCT02326272)	178	48
		CIMPACT (NCT02346240)	332	48
Etanercept	RA	160009	154	26
		160012	415	52
	PsO	20021639	486	24
		20021642	390	12
	PsA	16.0030 (NCT00317499)	101	24
	AS	16.0037	138	24
Golimumab	RA	GO-FORWARD (NCT00264550)	311	52
		GO-AFTER (NCT00299546)	306	24
		GO-BEFORE (NCT00264537)	474	52
	PsA	GO-REVEAL (NCT00265096)	292	52
	AS	GO-RAISE (NCT00265083)	277	24
	UC	PURSUIT-Maintenance (NCT00488631)	308	54
Guselkumab	PsO	VOYAGE 1 (NCT02207231)	329	48
		VOYAGE 2 (NCT02207244)	496	72
		NAVIGATE (NCT02203032)	135	28
	PsA	DISCOVER 1 (NCT03162796)	256	52
		DISCOVER 2 (NCT03158285)	493	100
Infliximab	RA	ATTRACT (NCT00269867)	340	54
	CD	ACCENT 1	573	54
		ACCENT 2	139	54
	UC	ACT 1 (NCT00036439)	243	54
		ACT 2 (NCT00096655)	241	30
	AS	P01522	35	12
	PsA	IMPACT	50	16
	PsO	SPIRIT	198	30
		EXPRESS	298	50
Ixekizumab	PsO	UNCOVER-1 (NCT01474512)	865	12
		UNCOVER-2 (NCT01597245)	698	12
		UNCOVER-3 (NCT01646177)	771	12
	PsA	SPIRIT-P1 (NCT01695239)	210	24
		SPIRIT-P2 (NCT02349295)	245	24
Risankizumab	PsO	ULTIMMA-1 (NCT02684370)	304	52
		ULTIMMA-2 (NCT02684357)	294	52
		IMMHANCE (NCT02672852)	407	28
		IMMVENT (NCT02694523)	301	44
Sarilumab	RA	MOBILITY (NCT01061736)	857	52
		TARGET (NCT01709578)	365	24
		MONARCH (NCT02332590)	184	24
Secukinumab	PsO	ERASURE (NCT01365455)	490	52
		FIXTURE (NCT01358578)	654	52
		FEATURE (NCT01555125)	118	52
		JUNCTURE (NCT01636687)	121	52
		SCULPTURE (NCT01406938)	966	52
		CLEAR (NCT02074982)	335	52
	PsA	FUTURE 1 (NCT01392326)	404	52
		FUTURE 2 (NCT01752634)	299	24
Tildrakizumab	PsO	reSURFACE 1 (NCT01722331)	617	64
		reSURFACE 2 (NCT01729754)	621	52
Tocilizumab	RA	AMBITION (NCT00109408)	389	24
		LITHE (NCT00106535)	797	52
		OPTION (NCT00106548)	418	24
		TOWARD (NCT00106574)	805	24
		RADIATE (NCT00106522)	338	24
Ustekinumab	PsO	PHOENIX 1 (NCT00267969)	510	40
		PHOENIX 2 (NCT00307437)	820	52
	PsA	PSUMMIT I (NCT01009086)	409	52
		PSUMMIT II (NCT01077362)	208	52
	CD	UNITI-1 (NCT01369329)	494	20
		UNITI-2 (NCT01369342)	418	20
	UC	UNIFI (UNIFI-I + UNIFI-M, NCT02407236)	642	52
Vedolizumab	UC	GEMINI 1 (NCT00783718)	746	52
	CD	GEMINI 2 (NCT00783692)	967	52
		GEMINI 3 (NCT01224171)	209	10
	AS	MEASURE 1 (NCT01358175)	249	52
		MEASURE 2 (NCT01649375)	145	52

Eligibility criteria to biologics of pivotal clinical trials (RCTs)

	RCT	Inclusion criteria	Exclusion criteria
Rheumatoid Arthritis			
Adalimumab	**ARMADA - DE009**	• **Age ≥ 18 years;** • Active disease was defined as the presence of at least 9 tender joints (of 68 joints evaluated) and 6 swollen joints (of 66 joints evaluated); • **Previously treatment with MTX for a minimum of 6 months** and must have been taking a stable weekly dose (12.5–25 mg, or 10 mg if intolerant to higher doses) for at least 4 weeks before entering the study; • **Previous failure treatment with ≥ 1 DMARD besides MTX, but no more than 4 DMARDs**.	• Standard exclusion criteria used in trials of other biologics in patients with RA; • **Prior treatment with anti-CD4 therapy or TNF-antagonists**; • History of active listeriosis or mycobacterial infection; • **Major episode of infection requiring hospitalization** or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days prior to screening.
	DE011	• Active disease defined as >12 tender joints based on a 68 joint assessment, >10 swollen joints based on a 66 joint evaluation, and either an erythrocyte sedimentation rate (ESR)>28 mm/1st h or a serum C reactive protein (CRP) concentration>20 mg/l; • **Previous failure treatment with at least one DMARD**; • Negative pregnancy test and the use of a reliable contraceptive method were mandatory in women of childbearing potential.	• Joint surgery within 2 months before screening; • **Infection requiring admission to hospital or treatment with intravenous antibiotics within 1 month before screening**; • **Previous treatment with either an intra-articular or intramuscular corticosteroid within 1 month before the study** or an investigational small molecule drug or biological agent within 2 months or 6 months before screening, respectively; • Impaired renal or hepatic function, or a **history of tuberculosis** as shown by radiographs.
	DE019 **(NCT00195702)**	• **Age ≥ 18 years;** • Good health (Investigator discretion) with a recent stable medical history; • Screening and baseline visits >=6 swollen joints and >=9 tender joints, despite a minimum of 3-months treatment with methotrexate (MTX). (Distal interphalangeal joints [DIPs] were not to be included in joint count for inclusion; • Screening and baseline visits could be 3 to 28 days apart for patients not previously receiving disease-modifying anti-rheumatic drugs [DMARDs] other than MTX or 4 to 6 weeks for patients requiring a DMARD washout period.); • Insufficient efficacy with **MTX** 12.5 to 25 mg per week (10 mg per week if MTX intolerant); • If patient on a second-line treatment (**DMARD**) other than MTX, he/she had to discontinue it for at least 28 days before the baseline visit (the washout period); • Treatment with oral folic acid 1-3 mg/day or, if appropriate, up to 10 mg leucovorin per week; • Both rheumatoid factor positivity and a C-reactive protein value >=1 mg/dL, or at least one joint erosion on X-ray.	• Subject considered by the investigator, for any reason, to be an unsuitable candidate for the study; • **Female subject who was pregnant or breast-feeding or considering becoming pregnant;** • **Preceding treatment with any tumor necrosis factor (TNF) antagonist, including adalimumab;** • Prior exposure to alkylating agents, such as chlorambucil or cyclophosphamide; * • **Intra-articular, intramuscular, or intravenous administration of corticosteroids within 4 weeks prior to the screening visit;** • Subject was wheelchair bound or bedridden.
	STAR or DE031	• **Age ≥ 18 years**; • Active RA at both screening and baseline visits defined by at least 6 swollen joints and at least 9 tender joints (excluding distal interphalangeal joints).	• Treatment with anti-CD4 therapy or **biologic DMARD** (e.g., TNF antagonists,interleukin-1 receptor antagonists); • History of an active inflammatory arthritide other than RA; • History of active listeriosis or mycobacterial infection**, a major episode of infection (i.e., infections requiring hospitalization,** treatment with intravenous **antibiotics within 30 days prior to screening**, or oral antibiotics within 14 days prior to screening).

Flow-chart of RW incident biologic users included in the study

Subjects registered in the study period (2010-2020):

N= 29,142,822

Tuscany: N= 3,726,338
Veneto: N= 4,902,866
Emilia-Romagna: N= 4,428,799
Friuli-Venezia-Giulia: N= 1,222,007
Lazio: N= 5,777,164
Apulia: N= 4,057,108
Sicily: N= 5,028,540

Patients with ≥ 1 biological drug dispensing approved for the treatment of IMIDs during the study period:

N= 88,067 (0.3%)

Tuscany: N= 13,916
Veneto: N= 14,821
Emilia-Romagna: N= 10,223
Friuli-Venezia-Giulia: N= 4,358
Lazio: N= 17,062
Apulia: N= 15,392
Sicily: N= 12,295

Incident* users of biological drugs during the study period:

N= 87,795 (99.7%)

Tuscany: N= 13,916
Veneto: N= 14,786
Emilia-Romagna: N= 10,174
Friuli-Venezia-Giulia: N= 4,303
Lazio: N= 17,002
Apulia: N= 12,273
Sicily: N= 15,341

Incident users of biological drugs with ≥1 year of database history pre- and post-ID:

N= 66,460 (75.7%)

Tuscany: N= 11,986
Veneto: N= 12,814
Emilia-Romagna: N= 9,647
Friuli-Venezia-Giulia: N= 3,529
Lazio: N= 14,362
Apulia: N= 6,468
Sicily: N= 7,654

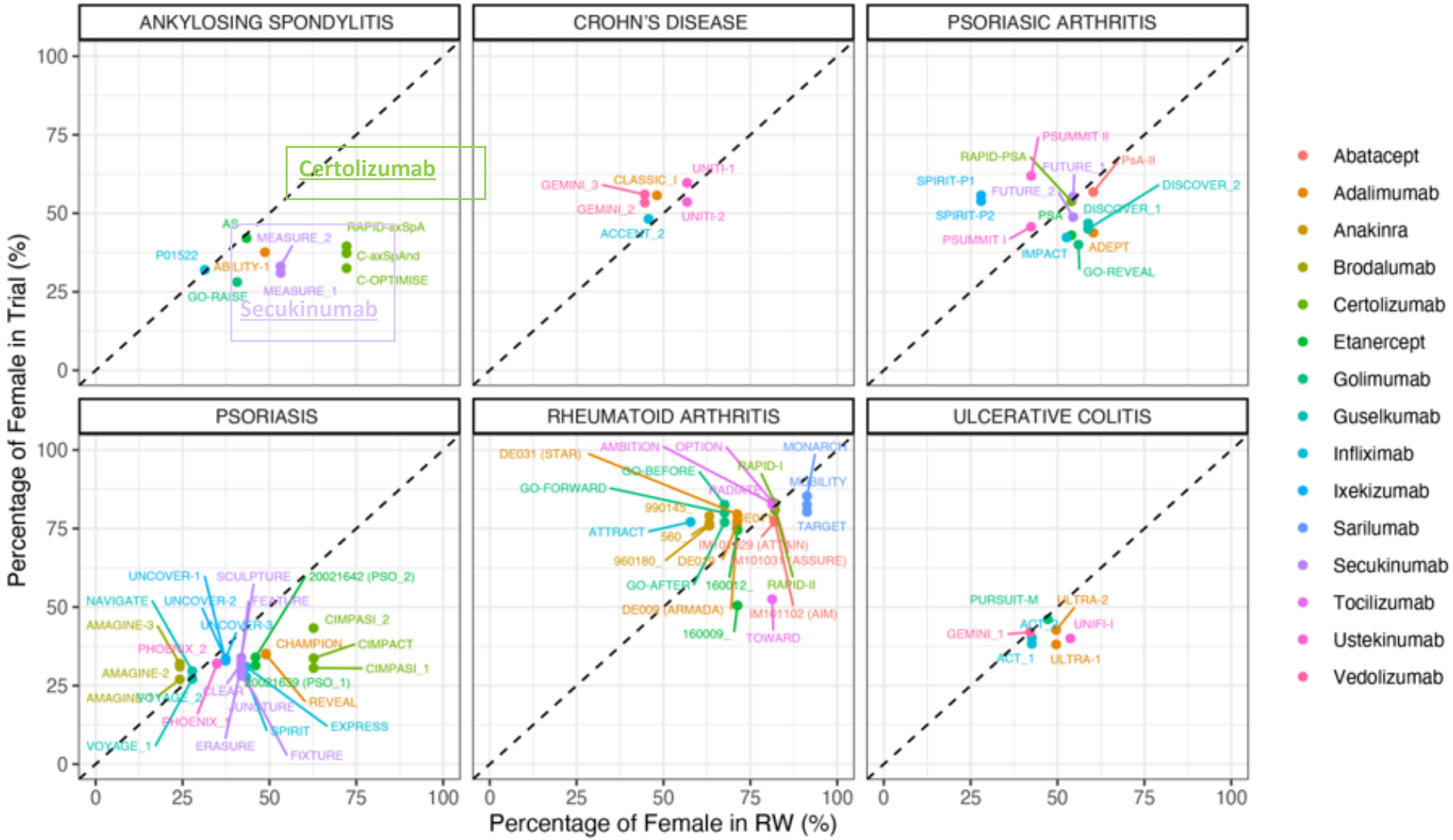
Incident users of biological drugs treated for IMIDs:

N= 57,208 (86.1%)

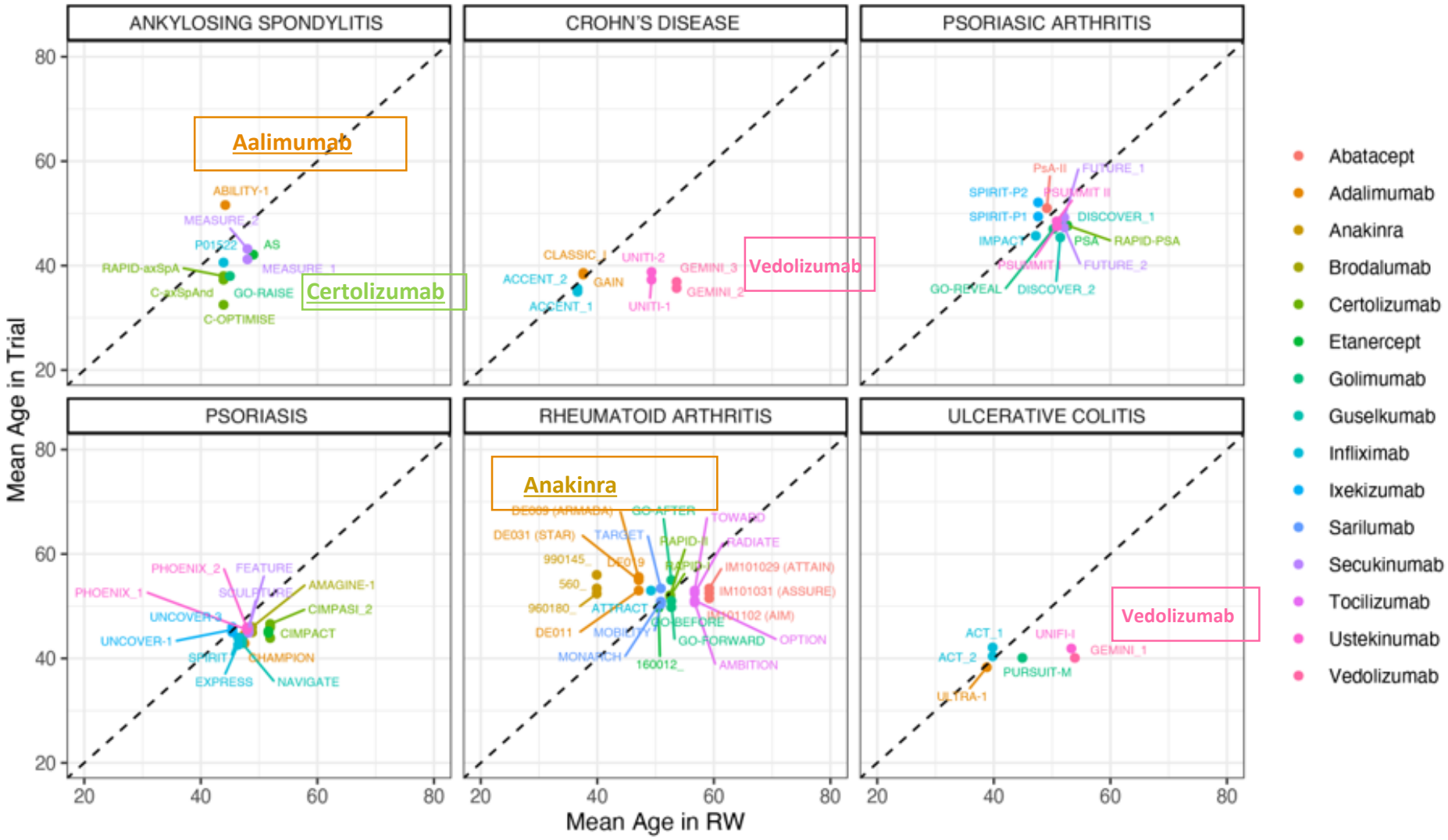
Tuscany: N= 9,547
Veneto: N= 11,735
Emilia-Romagna: N= 7,913
Friuli-Venezia-Giulia: N= 3,093
Lazio: N= 12,944
Apulia: N= 5,302
Sicily: N= 6,674

*Biological drug users without any dispensing any time prior to Index Date (ID);
IMIDs= Immune-Mediated Inflammatory Diseases

Comparison of the baseline characteristics of pivotal RCTs vs. RW population, stratified by individual drug and indication for use - *% of Females*



Comparison of the baseline characteristics of pivotal RCTs vs. RW population, stratified by individual drug and indication for use - *Mean age*



Anakinra – RA (RCT: 960180)

Etanercept – RA (RCT: 160009)

Inclusion criteria

- **Age ≥18 years;**
- Inadequate response (defined as discontinuation of therapy because of lack of effect) to **one to four DMARDs** (such as azathioprine, methotrexate, sulfasalazine, penicillamine, hydroxychloroquine, or oral or injectable gold);
- DMARD washout period that lasted at least 1 month before starting study drug treatment; no DMARDs were permitted during the study;
- Active disease at enrollment (before the DMARD washout period), defined as 12 or more tender joints, 10 or more swollen joints, and at least one of the following: erythrocyte sedimentation rate of at least 28 mm/h, C-reactive protein level greater than 20 mg/L, or morning stiffness for at least 45minutes;
- Concomitant therapy with stable doses of oral corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) was permitted;
- Corticosteroid doses could not exceed the equivalent of 10 mg of prednisone per day, and NSAID doses could not exceed the maximum dose recommended by the manufacturer.

Exclusion criteria

- Intra-articular corticosteroids during the study or beginning 4 weeks before enrollment.

- Receiving or has received any investigational drug within the previous 30 days or within 5 half-lives of any investigational drug, whichever is greater (or is currently using an investigational device)

Comparison of the distribution of incident biological drug users not eligible in pivotal RCTs vs. RW in RA, stratified by individual drug

	Patients treated for IMIDs in RW N	RW treated patients not eligible for RCTs N (%)
Rheumatoid arthritis		
Golimumab	1,705	722 (42)
		19 (1)
		703 (41)
Infliximab	1,761	955 (54)
Sarilumab	196	43 (22)
		79 (40)
		72 (37)
Tocilizumab	2,413	790 (38)
		268 (11)
		21 (1)
		899 (37)
		141 (6)

Study limitations

- Potential **misclassification** of the exact **indication for use** of **biological drug** in the RW setting;

- **Underestimated ineligible patients** to biologic treatment (limited traceability of inclusion/exclusion criteria defined by each pivotal RCT)

Conclusions

- **Baseline characteristics** of biologic users in **RW setting** are quite **different** from those of patients enrolled in **pivotal RCTs** (e.g., *higher mean age*);

- High proportion of incident biologic users not eligible to biologic treatment in RW;

- **Distributed multi-database networks**, such as VALORE project, collecting all routinely healthcare services provided to biologic users, may offer the opportunity to assess both short- and long- term **effectiveness and safety** of biologics in **real-world setting**.

Thank you!

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Thanks for your attention!

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Colleghi di tutte le Regioni partecipanti e area vigilanza post-marketing di AIFA!