# Drug utilization of biological drugs in patients over 65 years with Immune-mediated inflammatory diseases through the Italian VALORE network

## Summary



## Introduction

Scientific evidence has shown that biological drugs are effective for the treatment of various dermatological, rheumatological and gastroenterological immune mediated inflammatory diseases (IMIDs) such as crohn's disease (CD), ulcerative colitis (CU), rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis (PsO), spondylarthritis (AS).[1] The combination of an ageing world population and the chronic course of IMIDs results in an increased prevalence of elderly patients affected by these diseases.[2,3]

Biological drugs such as TNF-alpha inhibitors, anti-interleukin, selective immunosuppressant and anti-integrin represent an additional therapeutic option for the treatment of these diseases and still controversial evidence exists about comparative effectiveness and safety versus conventional disease modifying anti-rheumatic drugs (cDMARDs) in older patients.[4] Moreover, choosing the optimal type of treatment may be difficult in older patients, not only because of limited evidence on safety and efficacy coming from pivotal randomized clinical trials, but also because of possible complications of patient characteristics such as comorbidities, concomitant drug use,

polypharmacy, functional status and frailty. As an example, in the ORAL surveillance trial which included patients with more similar characteristics to the ones treated in real-world setting (rheumatoid arthritis patients aged 50 years or older with comorbidities), the occurrence of cancer and major adverse cardiovascular events with tofacitinib (non-biological drug) in such population was more frequent respect to the respective pivotal RCT.[4,5] This led to the updating of the Summary of Product Characteristics of tofacitinib which should be used in patients with cardiovascular or cancer risk factors only if no suitable treatment alternative are available. Therefore, it is possible that physicians are reluctant to prescribe certain systemic therapies such as biologic drugs in older patients, which could lead to undertreatment of this patient group. Moreover, as elderly patients are often excluded from clinical trials, only limited literature is available about how biological drugs are used in this specific population.[5]

The VALORE project multi-database network has access to data on more than 200,000 biological drug users with immune-mediated inflammatory diseases from 16 Italian regions. This network uses an R-based open-source tool "TheShinISS," developed by the Italian National Institute of Health for conduction of distributed analyses of the claims data of each region which participate in the project. Given the wide amount of data, this network used for post-marketing surveillance of biological drugs is suitable to conduct analysis on special populations such as elderly patients.[6]

Our large-scale, population-based study aims to describe the frequency of use and persistence to biological drugs in patients older than 65 years with IMIDs in the Italian real-world setting in the years 2010-2022 using the VALORE project distributed database network.

## Methods

*Data sources*

A retrospective, cohort, drug utilization study will be performed. Fully anonymized claims data from the VALORE multi-database network will be used. More details are available in another publication.[6] Concerning data about biological drugs, they are recorded using the anatomical therapeutic chemical (ATC) classification system and national drug code while indications for use and causes of hospitalizations and exemptions are coded using the ICD-9-CM. Italian regional claims databases have been shown to provide accurate and reliable information for pharmacoepidemiologic research on biological drugs, as documented by Trifirò at al.[6]

*Study population*

From the source population, all subjects with at least one biological drug dispensing (i.e., prevalent users) approved for the treatment of IMIDs (RA, AS, PsO, PsA, UC, CD) between January 1st, 2010 and December 31st, 2022 (or last available date) will be selected. Among them, all biological drug users with at least 1 year of history and 1 year of follow-up in the database will be identified. The date of the first biological drug dispensing will be defined as the Index Date, and only incident biologic users will be selected (no dispensing before the index date). Among them, only subjects aged ≥ 65 years old at the index date will be included. Then, among old users of biological drugs, all patients with the above-mentioned IMIDs indication will be eligible for the study cohort. As a patient could potentially start multiple biological drugs during the entire study period, the same patient could be included in different incident treatment groups, and multiple individual biologic-specific IDs for the same patient were allowed. Patients will be followed from the index date until the occurrence of one of the following events (whichever occurs first): a) patient's death; b) end of the study observational period or end of data collection.

*Exposure Assessment*

All biological drugs (both originators and biosimilars) available and approved in Italy for the treatment of the above-mentioned IMIDs during the study period will be included:

a) *TNF-alpha inhibitors:* adalimumab (L04AB04), certolizumab pegol (L04AB05), etanercept (L04AB01), golimumab (L04AB06) and infliximab (L04AB02);
b) *Interleukin inhibitors*: anakinra (L04AC03), brodalumab (L04AC12), guselkumab (L04AC16), ixekinumab (L04AC13), risankizumab (L04AC18), sarilumab (L04AC14), secukinumab (L04AC10), tildrakizumab (L04AC17), tocilizumab (L04AC07), and ustekinumab (L04AC05);
c) *Selective immunosuppressive agent:* abatacept (L04AA24)
d) *Anti-integrin: v*edolizumab (L04AG05).

Defined daily dose (DDD) will be used to define dispensation coverage of a single drug episode (see analysis plan for the calculation of adherence and persistence indicators).

*Analysis plan*

*Description of patient characteristics*

In the study cohort, the following baseline patient characteristics overall and stratified by drug class will be assessed:

- sex;
- age (categorized as follows: 65–69, 70-74, 75-79, 80-84 and 85+, mean ± standard deviation) at index date;
- months follow-up (median, interquartile range - IQR),
- biologic drug dispensed at index date;
- biosimilar or originator as index drug (n, %);
- indication of use: a specific META-algorithm was developed and validated; REF
- comorbidities: hypertension, ischemic heart disease, cerebrovascular disease, atrial fibrillation, diabetes, chronic renal failure, chronic liver disease, chronic pulmonary disease, previous transplant, previous infection evaluated any time prior to the index date;
- previous cDMARDs or indicated drugs categorized as previous use of immunosuppressants, nonsteroidal anti-inflammatory drugs, glucocorticoids, and Janus kinase inhibitors evaluated any time prior to the index date;
- concomitant use of cDMARDs and corticosteroids assessed in the 3 months after the index date;
- patients will be considered polymedication users if they have at least five or more different drug categories among the above-mentioned medications in the three months before the index date.

*Prevalence of biological drug use*

For each calendar year, the overall ratio of prevalent older users of biological drugs per 100.000 inhabitants will be calculated, with 95% confidence intervals, dividing the number of older patients receiving at least one study drug and the number of older residents during the observation period, stratified by age groups, sex, pharmacological class, biological drug, and single indication.

*Persistence to index biological drug*

If a subject has more than a 60-day treatment gap between the estimated end of exposure of the previous dispensing and the start of the next one (if any) or switched/swapped to another active ingredient, he/she will be defined as discontinuer. Persistence will be assessed at 12 and 24 months after the index date (stratification by single active ingredient, indication, type of index drug, sex, and age group). In such analysis, denominator will be considered as those patients with one year and two years of follow-up, respectively. Also, Kaplan Meier curves will be used to represent the cumulative % of persistent users all over the available follow-up. Patients will be censored in case of death and end of the study period. Additionally, a descriptive analysis will be conducted to evaluate the use of drugs acting on the immune system at 60 days from discontinuation (use of different biological drugs with respect to the index drug, JAK-inhibitors, cDMARDs, corticosteroids).

*Adjusted risk of discontinuation to the treatment at one year of follow-up*

Logistic regression models, one for each indication, will be carried out to identify predictors of discontinuation to biological drugs at one year. The following covariates will be included in the univariate models: sex, age class at index date (categorized as follows: 65–69, 70-74, 75-79, 80-84 and 85+), index drug, comorbidities (hypertension, ischemic heart disease, heart failure, cerebrovascular disease, atrial fibrillation, diabetes mellitus, chronic pulmonary disease, renal failure, chronic liver disease, previous transplant, previous infection, evaluated any time prior to the index date), previous use of immunosuppressant and no-immunosuppressant drugs and polypharmacy. The covariates that will be found to be statistically significant in the univariate analysis will be used to carry out the multivariate analysis.

*Statistical analysis*

Results will be presented as mean ± standard deviation (SD) or median with interquartile range depending on the underlying distribution for quantitative variables and will be summarized by absolute frequencies and percentages for categorical variables. Continuous and categorical variables will be compared across groups according to the pharmacological class at baseline using a t-test or Chi-Square test (or Fisher's exact test when appropriate) for continuous and categorical variables, respectively. As for the logistic regression model, results will be reported as an odds ratio with 95%CI and represented using forest plots. All statistical analyses will be performed using

R version 4.0 (The R Foundation for Statistical Computing, Vienna, Austria). The significance level for all statistical tests will be set at p-value < 0.05.

*Sensitivity analyses*

A gap of 45 days instead of 60 will be used to defined persistence.

## References


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