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ORIGINAL RESEARCH ARTICLE

Frequency of Biological Drug Use in Older Patients with Immune-Mediated Inflammatory Diseases: Results from the Large-Scale Italian VALORE Distributed Database Network

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Abstract

Background Limited real-world data on biological drug use in older patients with immune-mediated inflammatory diseases (IMIDs) exist despite these drugs carrying serious risks in this population.

Objective We aimed to describe the frequency and persistence of biological drug use in older patients (≥65 years) with IMID, including inflammatory bowel diseases (IBDs), psoriatic arthritis/psoriasis, rheumatoid arthritis (RA), and ankylosing spondylitis, in a large Italian population.

Methods A retrospective cohort study using the VALORE distributed claims database network from 13 Italian regions in the years 2010–2022 was performed. Older patients with IMID receiving biological drugs were included. Yearly prevalence of biological drug use and treatment persistence among incident users, from first dispensing to discontinuation/switching to another drug, was measured. Multivariable logistic regression was employed to identify treatment discontinuation predictors.

Results The prevalence of biological drug use in older patients with IMID increased dramatically from 2010 (0.44 per 1000 residents) to 2022 (2.48 per 1000 residents). Overall, 25,284 incident users of biological drugs were identified, with a female/male ratio of 1.6 and a mean age of 71.0 (standard deviation ±5.2) years. The median duration of follow-up was 4.2 (2.5–6.6) years, and the most common indication for use was RA ($n=8371$; 33.1%). Overall, biological drug persistence was 54.4% at 1 year from treatment start. The highest persistence rates were found for vedolizumab and ustekinumab in patients with IBD (ulcerative colitis, 68.1% and 76.2%, respectively; Crohn's disease, 69.6% and 88.1%, respectively). Polypharmacy, advanced age, and female sex were identified as predictors of treatment discontinuation.

Conclusions This study documented a significant rise in biological drug use among older patients with IMID in Italy over the last decade. Around 50% of users discontinued treatment after the first year, with even higher rates observed in very old patients with polypharmacy. These findings highlight potential concerns about the use of biological therapies in older patients and underscore the urgent need for large-scale cohort studies to address the current knowledge gaps regarding their safety and effectiveness in this vulnerable population.

1 Introduction

Immune-mediated inflammatory diseases (IMIDs) include a clinically different group of chronic conditions, such as psoriasis (PsO), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), and ankylosing spondylitis (AS), whose prevalence has increased in the last decades, particularly among the older population [1]. Biological drugs, such as tumor necrosis factor (TNF)-alpha inhibitors, anti-interleukins, selective immunosuppressant (abatacept), and anti-integrin (vedolizumab), represent commonly used pharmacological options for treating

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Key Points

The use of biological drugs in the older population with immune-mediated inflammatory disease has been rising dramatically, despite older patients not having been involved (or being very scarcely involved) in pivotal trials of biologics for IMID treatment.

The overall biologic drug treatment persistence rate among patients with IMID ≥ 65 years old at 1 year is around 50%, with more advanced age (> 80 years) and polypharmacy being independently associated with discontinuation within 1 year of treatment start.

This finding, together with a well-known increased susceptibility of very old patients with IMID to develop severe adverse reactions to biologics such as infections, questions the true benefit–risk profile of these drugs in this frailer population in real-world setting.

moderate-to-severe IMIDs. However, initiating a biological drug in older patients with IMID can be challenging for clinicians owing to increased susceptibility to potentially severe adverse drug reactions, the presence of contraindications, and the limited evidence on the benefit–risk profile of these drugs in the older population.

Older patients often exhibit altered pharmacokinetics and pharmacodynamics [2], which may affect the efficacy and safety of biological drugs, limiting the generalizability of findings from pivotal randomized clinical trials (RCTs) of biological drugs conducted in adult patients to the older population. A previous Italian study reported that patients treated with biological drugs in the real-world setting are substantially older than those enrolled in pivotal clinical trials [3], reflecting the limited inclusion of patients over 65 years old in pivotal RCTs of biological drugs [4]. Furthermore, in RCTs, the outcomes are typically evaluated over a short-term follow-up period, leaving a significant gap in information regarding long-term outcomes in older patients. A recently published meta-analysis showed that older users of biological drugs have an increased risk of infections compared with younger users, highlighting the need for large-scale real-world studies to assess the safety of biological therapy in older patients with IMID and informing clinical practice [5]. In addition, older patients often have concomitant health conditions, and polypharmacy further complicates the use of biological drugs by increasing the risk of drug–drug interactions, which can lead to increased toxicity or reduced efficacy [6]. Age-related physiological changes, such as reduced organ function and altered immune responses, can also exacerbate these challenges, further complicating the safe and effective use of biological therapies.

An earlier analysis of the VALORE distributed database network reported that the age-adjusted yearly prevalence of biological drug users increased threefold, from 0.7 per 1000 inhabitants in 2010 to 2.1 per 1000 inhabitants in 2019, highlighting a growing trend in the use of these therapies [7]. However, to date, no studies have specifically focused on the older population, leaving a gap in understanding the real-world utilization patterns of biological drugs in this subpopulation.

To address this gap, our large-scale, population-based study aims to describe the pattern of use and persistence of biological drugs, specifically in patients with IMID aged 65 years and older in Italian real-world setting from 2010 to 2022. In addition, the study investigates whether common conditions in older patients with IMID, such as polypharmacy and comorbidities, influence the discontinuation of biological drugs.

2 Material and Methods

2.1 Study Design

This was a retrospective, population-based, drug-utilization study, and it was performed using the Italian VALORE project distributed database network, which has been described previously [7]. The study protocol was registered in the Heads of Medicines Agencies-European Medicines Agency (HMA-EMA) catalogue of real-world data sources and studies (EUPAS1000000211), and, as part of the VALORE project, it was approved by the Ethical Committee of Verona and Messina Academic Hospital.

2.2 Data Sources

VALORE distributed database network collected fully anonymized claims data from 13 Italian regions (Abruzzo, Emilia-Romagna, Friuli-Venezia-Giulia, and Tuscany: years 2010–2022; Lombardy and Marche: years 2010–2021; Calabria: years 2020–2022; Lazio: years 2010–2020; Apulia: years 2014–2022; Sardinia: years 2012–2022; and Sicily, Veneto, and Umbria: years 2011–2022) covering about 46 million inhabitants (77.3% of the Italian population). Specifically, this data source collected the following information regarding biological drug users: hospital discharge records, drug dispensing from outpatient and hospital pharmacies, exemption from healthcare service co-payment, inhabitant registry, and outpatient encounter data [7]. In regional administrative data, biological drugs are coded using the Anatomical Therapeutic Chemical (ATC) classification system and national drug code, while causes

of hospitalizations and exemptions from co-payments are coded using the International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM). Administrative data do not collect information on the indication for use of drugs. Thus, the indications of biological drugs were retrieved through a validated META-algorithm developed in the context of the VALORE project [8].

2.3 Study Population

From the source population, all patients receiving at least one biological drug dispensing approved for the treatment of studied IMIDs (i.e., CD, UC, PsA, PsO, RA, and AS) between 1 January 2010 and 31 December 2022, were identified (i.e., prevalent users). Only subjects aged ≥ 65 years old during the observation period were included. Among them, all incident biological drug users (no dispensing of biological drug any time prior to the treatment start date, i.e., index date) with at least 1 year of look back period and 1 year of follow-up in the database were selected. Patients were followed from the index date until the occurrence of one of the following events (whichever occurred first): (a) patient's death; (b) emigration from the region; or (c) end of the study period or end of data collection. As a patient could potentially initiate multiple treatments with biological drugs at different time points during the entire study period, we also identified incident treatments (no dispensing of the same active ingredient during the available look-back period). Each incident treatment was classified according to the chronological order of dispensing in the same patient (i.e., first line, second line, third and further line).

2.4 Study Drugs

The following biological drugs approved in Italy for the treatment of the IMIDs mentioned above during the study period were included: TNF-alpha inhibitors: adalimumab (L04AB04, both originators and biosimilars), certolizumab pegol (L04AB05), etanercept (L04AB01, both originators and biosimilars), golimumab (L04AB06) and infliximab (L04AB02, both originators and biosimilars); anti-interleukins: anakinra (L04AC03), brodalumab (L04AC12), guselkumab (L04AC16), ixekizumab (L04AC13), risankizumab (L04AC18), sarilumab (L04AC14), secukinumab (L04AC10), tildrakizumab (L04AC17), tocilizumab (L04AC07), and ustekinumab (L04AC05); selective immunosuppressive agent: abatacept (L04AA24); and anti-integrin: vedolizumab (L04AG05). Since rituximab is mainly used for hematological malignancy [9, 10], this drug was not included in this study. Moreover, mirikizumab and bimekizumab were not considered since, at the end of the study period, these drugs were not reimbursed by the Italian National Healthcare System yet.

The approval dates of each biological drug included in this study were reported in Supplementary Table S1 according to the respective indication for use.

2.5 Statistical Analysis

Demographic and clinical characteristics of older incident users of biological drugs, stratified by pharmacological class, were evaluated and presented as mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables and were summarized as percentages for categorical variables. For each calendar year, the prevalence of biological drug use among older patients as rate per 1000 residents with a 95% confidence interval (CI) was calculated, dividing the number of older patients receiving at least one biological drug by the number of older residents during the same observation period (data were retrieved from the Italian National Institute of Statistics–ISTAT [11]), stratified by age group, sex, pharmacological class, individual compound, and single indication for use.

The accuracy of the applied META-algorithm for indication of use identification is not 100%. As such, biological drug users with a missing indication or those mistakenly assigned an unapproved indication on the basis of the respective summary of product characteristics were excluded from the subsequent analyses. The distribution of incident treatments in older people with IMID stratified by calendar year, treatment line, molecule, and indication for use was described. Persistence (days) to the first-line biological drug over time was assessed and stratified by indication for use, age group, and sex. The number of days covered for each biological drug dispensing was calculated on the basis of defined daily doses (DDDs) [12]. The biological drug users were considered discontinuers if no further dispensing was recorded within 60 days of the grace period following the last day of biological drug coverage. As some of the biological drugs should be started with loading doses, no stockpiling was considered to avoid overestimation of the treatment coverage by using DDD. Patients were censored in case of death and end of the study period. A Kaplan–Meier curve was used to describe the treatment persistence. In the case of switching to a different biological drug, the patient was also considered a discontinuer of the index drug (the date of the first dispensing of the new drug was considered as the discontinuation date). To better distinguish between those stopping any treatment for IMID from those who switched to other drugs approved for IMID treatment, we measured the proportion of discontinuers who started within 60 days from the discontinuation date of any of those drugs. This included either a different biological drug, Janus kinase inhibitors (JAKi), conventional disease-modifying antirheumatic drugs (cDMARDs), or corticosteroids.

Finally, logistic regression models were carried out to identify predictors of biological drug treatment

discontinuation at one year, specifically for each indication for use. The following covariates were initially included in the univariate models: sex; age class at index date (categorized as follows: 65–69, 70–74, 75–79, 80–84 and ≥ 85 years); 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 other drugs of interest; as well as polypharmacy (received at least five different pharmacological classes within the 3 months prior to the start of the biological treatment). The covariates that were statistically significantly associated with treatment discontinuation in the univariate analysis were retained in the final multivariate analysis. The results were reported as odds ratio (OR) together with 95% CI and graphically represented using forest plots. The significance level for all statistical tests was set at p-value < 0.05. All statistical analyses were performed using the publicly available R software environment (version 4.3.0).

3 Results

3.1 Prevalence of Biological Drug Use

During the years 2010–2022, overall, 45,211 prevalent users who were ≥ 65 years old were identified (Fig. 1). The prevalence of biological drug use in older patients showed a significantly increasing trend over the study period (+463.6%), ranging from 0.44 per 1000 residents in 2010 to 2.48 per 1000 residents in 2022. Biological drug use has been consistently higher among older women than older men throughout the study period (Fig. 2a), with a constant increase for both sexes over time. The prevalence of biological drug use stratified by age group is reported in Fig. 2b. TNF-alpha inhibitors have been the most widely used class of biological drugs in older patients, showing a consistent upward trend over the study period (Supplementary Fig. S1a). The greatest increase was observed for adalimumab (0.13 to 0.62 per 1000 residents), as shown in Supplementary Fig. S1b. The prevalence of biological drug use stratified by indication was also reported in Supplementary Fig. S2.

3.2 Characterization of Incident Users of Biological Drugs and Incident Treatments

Overall, 25,284 older patients with IMID who were incident users of biological drugs were identified, with a total of 33,632 incident treatments that were initiated during the study period (Fig. 1).

Regarding the characteristics of those users, a female/male ratio of 1.6 and a mean age of 71.0 (SD ± 5.2) years was observed. The median duration of follow-up was 4.2 (2.5–6.6) years. At the index date, most of the incident users received adalimumab (n = 5667; 22.4%), followed by etanercept (n = 5638; 22.3%) and abatacept (n = 2772; 11.0%). The most common indications for use were RA (n = 8371; 33.1%) and PsO (n = 5526; 21.9%), even if indication for use was not accurately identified in around 18% of users. Around one quarter of missing indications concerned tocilizumab. Among comorbidities, the most frequent was hypertension (78.4%), followed by diabetes mellitus (20.6%). Overall, previous use of nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids for systemic use, and cDMARDs was found in 86.0%, 84.3%, and 80.6% of incident users, respectively. Instead, the use of JAKi prior to the treatment with the index biological drug was found in less than 1% (n = 193) of incident users. Around two thirds of incident users were on polypharmacy within the 3 months prior to the start of the biological treatment (Table 1).

Figure 3 shows the distribution of incident treatments with biological drugs stratified by calendar year, treatment line, molecule, and indication for use. The frequency of use of anti-interleukin drugs was lower among first-line incident treatments than among second- and further-line treatments. In comparison, the frequency of use of TNF-alpha inhibitors was higher among first-line incident treatments. Over the years, for all indications, the proportion of first-line use of TNF-alpha decreased, while the proportion of first-line use of anti-interleukin increased. A slight deflection in the frequency of use was observed between 2019 and 2020 in relation to the beginning of the coronavirus disease-2019 (COVID-19) pandemic in Italy.

3.3 Persistence to the First-Line Biological Drug over Time

Overall, during the first year of treatment, about half (54.4%) of older patients who were newly treated with biological treatment were still on the index drug, while this proportion decreased to 36.5% and 16.9% at 2 and 5 years of follow-up, respectively. The highest median time to treatment discontinuation was observed for vedolizumab (686 days, IQR [622; 749], anti-interleukins (535 days, IQR [511; 559]) and abatacept (446 days, IQR [417; 477]) versus TNF-alpha inhibitors (375 days (IQR: [365; 387]). Figure 4 shows the time to discontinuation of first-line biological treatment according to indication for use. As for PsO/PsA, patients initiating ustekinumab treatment reported higher persistence than other biological treatments. As for inflammatory bowel diseases (IBD), patients starting treatment with vedolizumab and ustekinumab showed higher treatment persistence than other biological drug users at 1 year (UC, 68.1% and 76.2%,

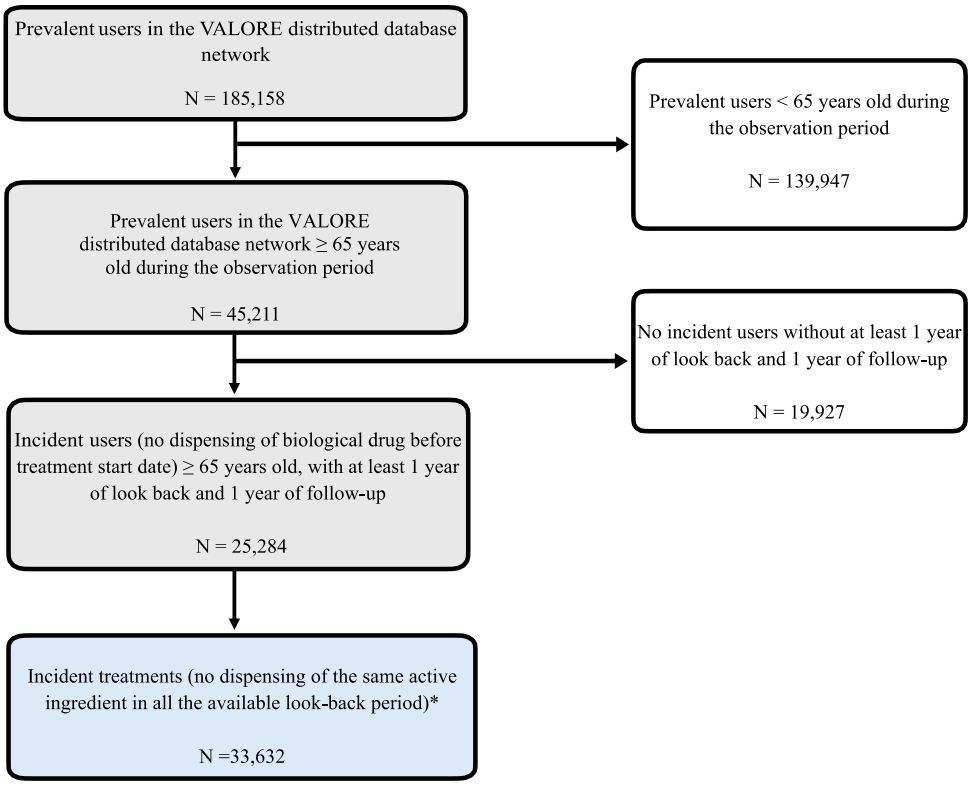

Fig. 1 Flowchart of older patients who were treated with biological drugs approved for IMIDs in the years 2010–2022. *As a patient could potentially initiate multiple treatments with biological drugs at different time points during the entire study period, we also identified incident treatments (no dispensing of the same active ingredient during the available look-back period). Each incident treatment was classified according to the chronological order of dispensing in the same patient (i.e., first line, second line, third and further line)

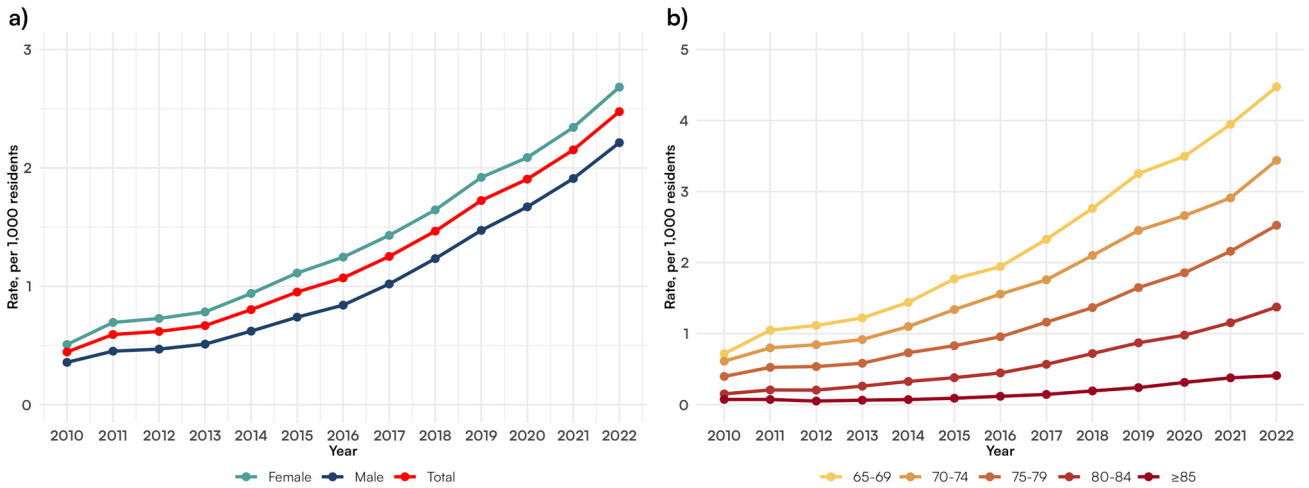

Fig. 2 Yearly prevalence of biological drug use in Italian older patients with IMID from 2010 to 2022, stratified by sex and age groups

respectively; CD, 69.6% and 88.1% respectively) while users of golimumab (approved only for UC) reported the lowest median time to discontinuation (282 days [236; 395]). As for the rheumatological area, patients showed rather comparable treatment persistence rates across different molecules except for secukinumab (approved only for AS), reporting the lowest median time to discontinuation of 260 days [IQR 231; 413]. Moreover, the very elderly patients discontinued treatment earlier than the younger ones (85+ years: 194 days, IQR [140; 232]; 80–84 years: 303 days, IQR [266; 334], with respect to the youngest (65–69 years: 484 days, IQR [467; 499]; 70–74 years: 424 days, IQR [405; 443]; and 75–79 years: 391 days, IQR [364; 417]) (Supplementary Fig. S3b).

In the 60 days following the treatment discontinuation date, a switch to another biological drug was found in 18% of discontinuers (switchers: 9.7%; swappers: 8.3%), while 13.6%, 5.4%, and 1.2% of patients used glucocorticoids, cDMARDs and JAKi, respectively (Supplementary Table S2).

3.4 Risk of Treatment Discontinuation at 1 Year of Follow-Up

Finally, Fig. 5 reported the risk of treatment discontinuation at 1 year of follow-up, stratified by indication for use. As compared with incident users of adalimumab, in patients with RA, those starting etanercept (OR 0.81 [95%CI 0.71–0.93]), abatacept (OR 0.76 [95% CI 0.66–0.87]) and tocilizumab (OR 0.72 [95% CI 0.61–0.85]) had a lower risk of discontinuation. A lower risk of discontinuation was also observed among incident users of ustekinumab for PsO (OR 0.45 [95% CI 0.37–0.54]) and PsA (OR 0.50 [95% CI 0.33–0.76]) indications (this also holds true for secukinumab users with PsO: OR 0.66 [95% CI 0.55–0.78]). Vedolizumab users with UC and CD had a lower risk of discontinuation (OR 0.57 [95% CI 0.43–0.77] and OR 0.72 [95% CI 0.55–0.95], respectively) than those starting with adalimumab. A reduced risk was also observed for ustekinumab users with UC [OR 0.25 (95% CI 0.15–0.42]). Conversely, those patients with UC starting biological treatment with golimumab had a higher risk of discontinuation (OR 1.72 [95% CI 1.06–2.82]). In patients with RA, previous use of cDMARDs was associated with a lower risk of biological drug discontinuation (OR 0.75 [95% CI 0.63–0.90]). Finally, polypharmacy was associated with a significantly higher risk of discontinuation in all indications of use except for AS.

4 Discussion

To the best of our knowledge, this is the largest population-based drug utilization study on biological drugs in older patients with IMIDs that was conducted in Europe and in Italy, specifically. At the same time, outdated evidence exists outside the European setting [13]. As for the Italian setting, only one study conducted at 47 Italian IBD centers (2013–2018), which included about 200 patients with inflammatory bowel diseases, was found [14].

From 2010 to 2022, we observed approximately a sixfold increase in the use of biologic drugs among older individuals with IMIDs, particularly those affected by RA and PsO. This trend aligns with evidence suggesting an increase in the prevalence of IMIDs in individuals aged over 60 years [15], which, as expected, has led to a corresponding rise in biological drug use. In addition, the extension of indications for biological drugs over this period has likely contributed to this increase.

Biological drugs more frequently prescribed in older patients were adalimumab and etanercept, with a notable increase in the prevalence of adalimumab use following the approval of its biosimilar. This increase is in line with regional guidelines recommending the use of the biologic with the lowest cost when safety and efficacy are comparable [16–18]. Accordingly, an Italian retrospective observation study on 89 patients aged ≥ 65 years demonstrated that adalimumab and etanercept were appropriate for the long-term management of older patients affected by psoriasis and psoriatic arthritis, showing a good benefit and risk profile [19]. However, the proportion of patients using TNF-alpha inhibitors as first-line treatment slightly declined over the study period, likely reflecting the more recent approval and increasing adoption of anti-interleukin and anti-integrin therapies as first-line options in older patients.

Notably, a slight decrease in biological drug use was observed between 2019 and 2020, probably as an effect of the COVID-19 pandemic. Another Italian study documented reduced biological drug use in patients with IMID in 2020 because of the COVID-19 pandemic [20]. These findings can be related to (1) concerns about the use of immune-modulating therapies in patients with IMID owing to the increased risk of severe acute respiratory syndrome-coronavirus-2 (SARS-COV-2) infection during the pandemic, as well as (2) logistical difficulties in accessing the hospitals for the management of chronic autoimmune diseases [20].

Our large-scale cohort study also reported information on more than 1900 patients over the age of 80 years who have been excluded from pivotal clinical trials of biological drugs in IMID. In scientific literature, no information on the efficacy and safety of biological drugs in this population is still available, and cohort studies of very old patients receiving biologics should be carried out urgently [3]. Moreover, polypharmacy is a common condition in the older population. Differences in the frequency of polypharmacy were found according to first-line biological therapy (i.e., patients taking abatacept or TNF-alpha inhibitors reported higher polypharmacy at baseline with respect to those patients starting with vedolizumab); polypharmacy is more common in RA, for which these drugs are approved, unlike vedolizumab [21, 22].

Notably, in contrast with the clinical guidelines' recommendation for each IMID, we observed 193 (less than 1%) patients receiving at least one JAKi dispensing before starting biological treatment. According to a recently published study reporting an increased risk of major adverse cardiovascular events (MACE) and malignancies in patients aged 50 years and older receiving JAKi [23], regulatory agencies, such as the European Medicines Agency (EMA) and Food and Drug Administration (FDA), issued warnings [24, 25] recommending the restricted use of JAKi in older patients or those with pre-existing risk factors for cardiovascular disease or cancer.

Our findings highlighted that, overall, 50% of patients discontinue treatment with biological drugs after 1 year. However, differences were observed according to the indication of use and biological drug. Patients with IBD starting with ustekinumab (n = 180) or vedolizumab (n

Table 1 Baseline characteristics of older incident users during the years 2010–2022, stratified by pharmacological class

Characteristics	Overall $N=25,284$	TNF-alpha inhibitors $N=14,974$	Anti-interleukins $N=6255$	Selective immunosuppressant $N=2772$	Anti-integrin $N=1283$
Sex, *n* (%)					
Female	15,659 (61.9)	9412 (62.9)	3612 (57.7)	2154 (77.7)	481 (37.5)
Male	9625 (38.1)	5562 (37.1)	2643 (42.3)	618 (22.3)	802 (62.5)
Mean age, years (SD)	71.0 (5.2)	70.8 (5.1)	71.1 (5.5)	71.6 (5.1)	71.5 (5.1)
Age categories, *n* (%)					
65–69	12,191 (48.2)	7447 (49.7)	3067 (49.0)	1131 (40.8)	546 (42.6)
70–74	7241 (28.6)	4301 (28.7)	1665 (26.6)	867 (31.3)	408 (31.8)
75–79	3908 (15.5)	2209 (14.8)	936 (15.0)	541 (19.5)	222 (17.3)
80–84	1507 (6.0)	790 (5.3)	433 (6.9)	196 (7.1)	88 (6.9)
≥ 85	437 (1.7)	227 (1.5)	154 (2.5)	37 (1.3)	19 (1.4)
Median follow-up, years (IQR)	4.2 (2.5–6.6)	4.8 (2.7–7.4)	3.4 (2.1–5.1)	4.6 (2.8–6.7)	3.0 (2.0–4.3)
Index drug, *n* (%)					
Adalimumab	5667 (22.4)	5667 (37.8)	–	–	–
Certolizumab	931 (3.7)	931 (6.2)	–	–	–
Etanercept	5638 (22.3)	5638 (37.7)	–	–	–
Infliximab	1419 (5.6)	1419 (9.5)	–	–	–
Golimumab	1319 (5.2)	1319 (8.8)	–	–	–
Abatacept	2772 (11.0)	–	–	2772 (100.0)	–
Vedolizumab	1283 (5.1)	–	–	–	1283 (100.0)
Secukinumab	1437 (5.7)	–	1437 (23.0)	–	–
Ustekinumab	1097 (4.3)	–	1097 (17.5)	–	–
Tocilizumab	2347 (9.3)	–	2347 (37.5)	–	–
Others[a]	1374 (5.4)	–	1374 (22.0)	–	–
Type of index drug, *n* (%)					
Biosimilar	5453 (21.6)	5453 (36.4)	–	–	–
Originator	19,831 (78.4)	9521 (63.6)	6255 (100.0)	2772 (100.0)	1283 (100.0)
Indication, *n* (%)					
Psoriasis	5526 (21.9)	3253 (21.7)	2273 (36.3)	–	–
Psoriatic arthritis	2919 (11.5)	2054 (13.7)	483 (7.7)	382 (13.8)	–
Crohn's disease	1444 (5.6)	802 (5.4)	159 (2.6)	–	483 (37.6)
Ulcerative colitis	1485 (5.8)	750 (5.0)	21 (0.3)	–	714 (55.7)
Rheumatoid arthritis	8371 (33.1)	4898 (32.7)	1432 (22.9)	2041 (73.6)	–
Ankylosing spondylitis	858 (3.4)	749 (5.0)	109 (1.8)	–	–
Hidradenitis suppurativa	7 (0.1)	7 (0.1)	–	–	–
Uveitis	43 (0.2)	37 (0.2)	6 (0.1)	–	–
Missing or not correct identifying indication	4631 (18.3)	2424 (16.2)	1772 (28.3)	349 (12.6)	86 (6.7)
Comorbidities, *n* (%)					
Hypertension	19,833 (78.4)	11,562 (77.2)	5085 (81.3)	2186 (78.9)	1000 (77.9)
Ischemic heart disease	2038 (8.1)	1046 (7.0)	611 (9.8)	237 (8.5)	144 (11.2)
Heart failure	1035 (4.1)	520 (3.5)	306 (4.9)	124 (4.5)	85 (6.6)
Cerebrovascular disease	1344 (5.3)	733 (4.9)	378 (6.0)	153 (5.5)	80 (6.2)
Atrial fibrillation	1079 (4.3)	520 (3.5)	335 (5.4)	122 (4.4)	102 (8.0)
Diabetes mellitus	5200 (20.6)	2958 (19.8)	1458 (23.3)	517 (18.7)	267 (20.8)
Renal failure	745 (2.9)	383 (2.6)	244 (3.9)	54 (1.9)	64 (5.0)
Chronic liver disease	1113 (4.4)	628 (4.2)	290 (4.6)	106 (3.8)	89 (6.9)
Chronic pulmonary disease	1297 (5.1)	643 (4.3)	382 (6.1)	180 (6.5)	92 (7.2)
Previous transplants	57 (0.2)	36 (0.2)	15 (0.2)	4 (0.1)	2 (0.2)

Table 1 (continued)

Characteristics	Overall $N=25,284$	TNF-alpha inhibitors $N=14,974$	Anti-interleukins $N=6255$	Selective immunosuppressant $N=2772$	Anti-integrin $N=1283$
Previous infections	2195 (8.6)	1116 (7.5)	582 (9.3)	276 (10.0)	221 (17.2)
Previous use of drug acting on immune-system, *n* (%)[b]					
cDMARDs	20,375 (80.6)	12,159 (81.2)	4398 (70.3)	2581 (93.1)	1237 (96.4)
Janus kinase inhibitor	193 (0.8)	96 (0.6)	57 (0.9)	40 (1.4)	–
NSAIDs	21,732 (86.0)	12,922 (86.3)	5328 (85.2)	2561 (92.4)	921 (71.8)
Glucocorticoids	21,310 (84.3)	12,486 (83.4)	5106 (81.6)	2591 (93.5)	1127 (87.8)
Concomitant use of cDMARDs, *n* (%)[c]	7250 (28.7)	4635 (31.0)	1,117 (17.9)	1361 (49.1)	137 (10.7)
Concomitant use of glucocorticoids, *n* (%)[c]	4038 (16.0)	2440 (16.3)	828 (13.2)	674 (24.3)	96 (7.5)
Polypharmacy within the previous 3 months, *n* (%)[d]	16,704 (66.1)	10,362 (69.2)	3698 (59.1)	2016 (72.7)	628 (48.9)

cDMARDs conventional disease-modifying antirheumatic drugs, *IQR* interquartile range, *NSAIDs* nonsteroidal antiinflammatory drugs, *SD* standard deviation, *SmPC* summary of product characteristics

[a]Others, anakinra ($n=251$), brodalumab ($n=115$), guselkumab ($n=221$), ixekizumab ($n=384$), risankizumab ($n=116$), sarilumab ($n=230$), tildrakizumab ($n=57$)

[b]Previous drug use evaluated at any time before index date

[c]Concomitant use of cDMARDs and glucocorticoids, assessed in the 3 months after index date

[d]Polypharmacy, five or more different pharmacological classes within the 3 months prior to the start of the biological treatment

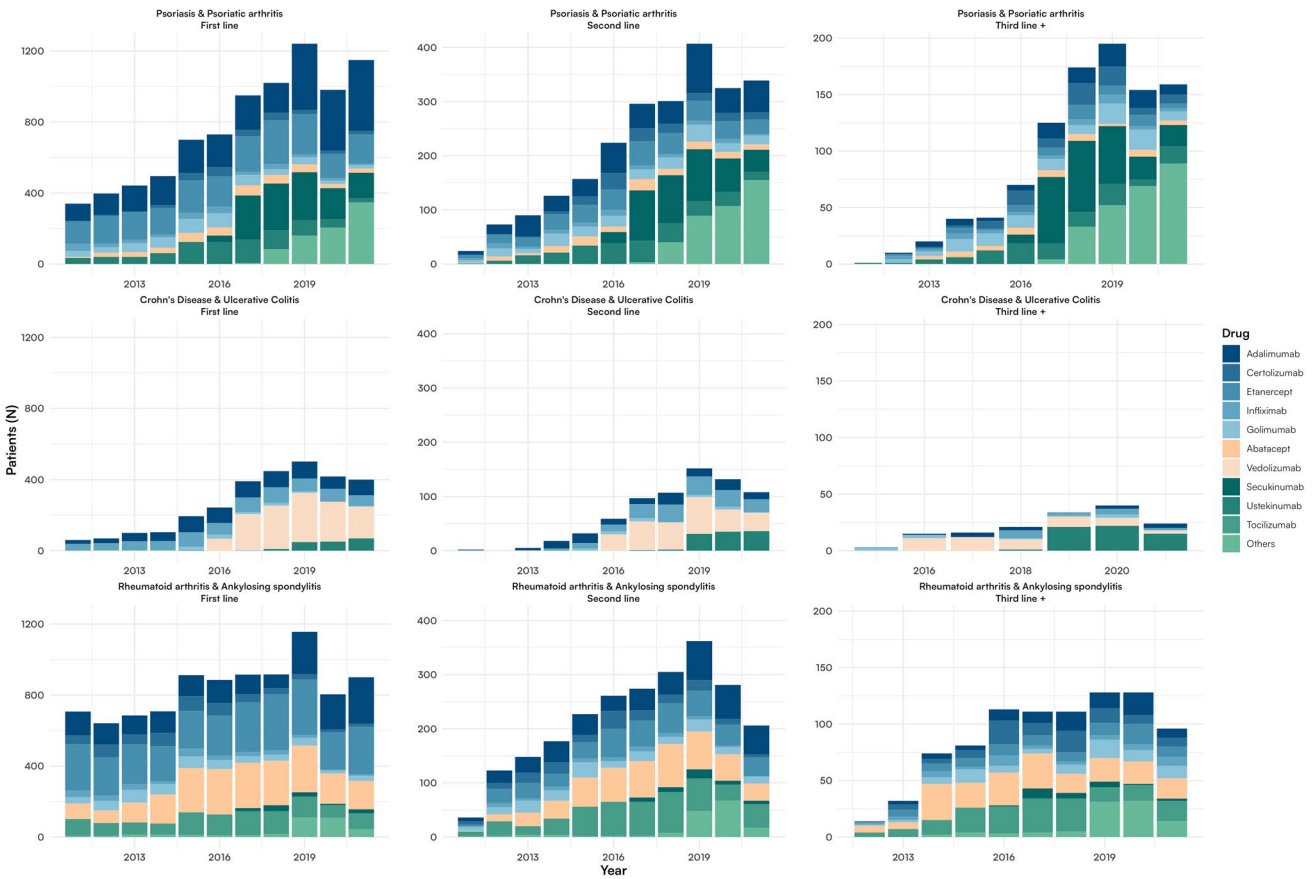

Fig. 3 Distribution of incident treatments with biological drugs in older people with IMID stratified by calendar year, treatment line, molecule and indication for use

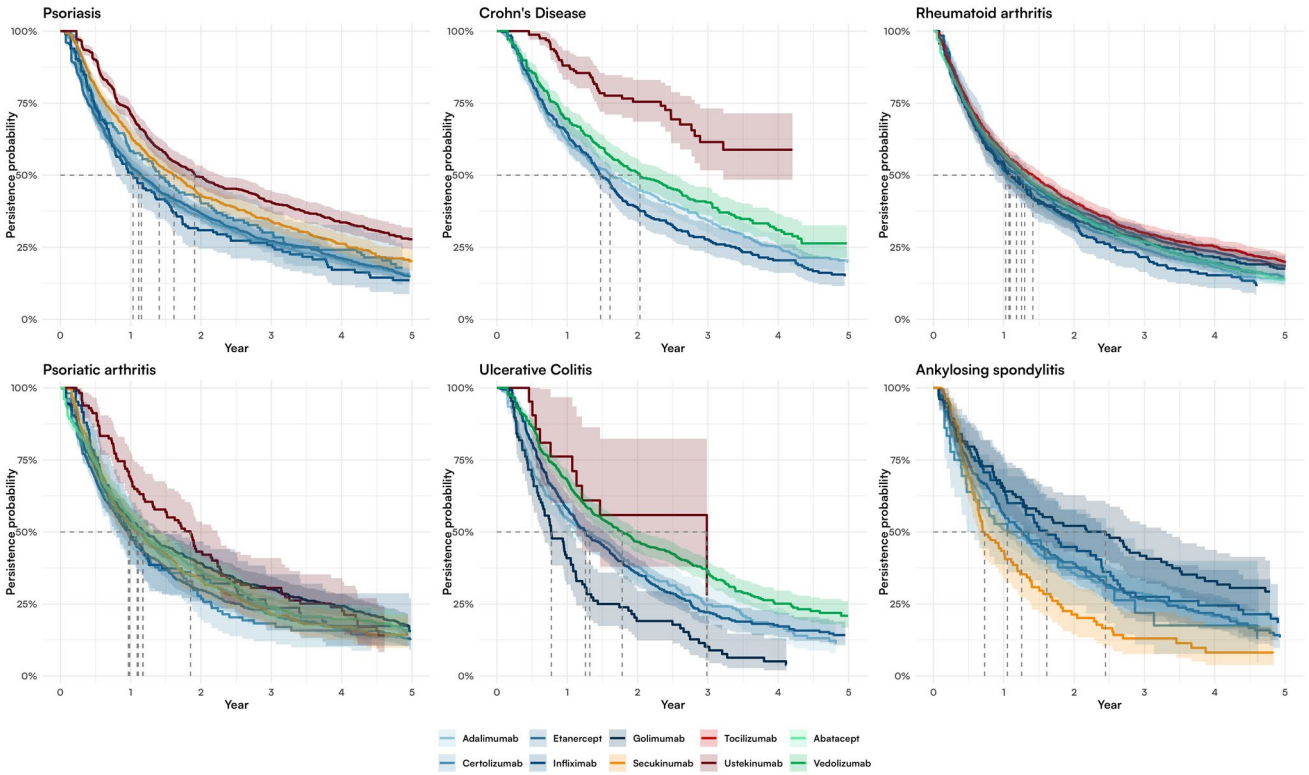

Fig. 4 Time to discontinuation of biological drugs among the first line of incident treatments, stratified by indication for use

= 1197) showed the highest persistence to treatment. According to EMA recommendations, both these drugs should be used when conventional therapy or TNF-alpha inhibitors are ineffective, no longer effective, or cannot be tolerated by the patient [26, 27]. Consequently, their use as first-line treatments should be limited, especially considering that, with the introduction of biosimilars, off-patent TNF-alpha inhibitors are generally more economical than more recently approved biological drugs. However, existing studies have not established a preferred sequencing order of biological therapies for patients with IBDs [28, 29]. Nonetheless, evidence from literature highlights the favorable profile of ustekinumab and vedolizumab in the older population. For instance, a retrospective study of older patients with Crohn's disease conducted in Canada between January 2000 and January 2020, suggests that ustekinumab is an effective and safe biological option for older patients [30], while another study conducted across four UK centers found comparable safety and efficacy compared with TNF-alpha inhibitors [31]. Similarly, a multicenter, multinational retrospective study conducted on 111 patients with vedolizumab and 60 patients with ustekinumab above the age of 60 years demonstrated comparable effectiveness and a favorable safety profile in older patients with IBDs [32]. Another recent study supports considering vedolizumab and ustekinumab as potential first-line treatment options for moderate-to-severe IBD in older patients [33], despite other aspects that were not considered in this study (i.e., health care expenses), which should be taken into account. These results were also confirmed by studies conducted in the adult population, reporting favorable safety [34] and efficacy [35] profiles for both drugs, even if real-world evidence found in literature is mainly related to second- or further-line treatment [36–38]. Finally, the recently published guidelines regarding the management of moderate-to-severe UC suggest that vedolizumab may be preferred among agents of similar efficacy in patients particularly vulnerable to infectious complications, such as older frail adults [39].

Several factors were found to have a potential impact on discontinuation of the first-line of biological drug at 1 year of follow-up: patients with polypharmacy and female and older patients were commonly reported to have an increased risk of discontinuation. Female sex was also previously reported as a predictive factor for discontinuation of biological therapies for psoriasis, confirming our study's results [40]. As van der Schoot et al. reported, the higher discontinuation rates among females may be partially explained by a greater incidence of adverse events, such as infections [40]. In addition, other studies have shown that female patients experience a higher symptomatic disease burden than males, along with a greater impact on mental

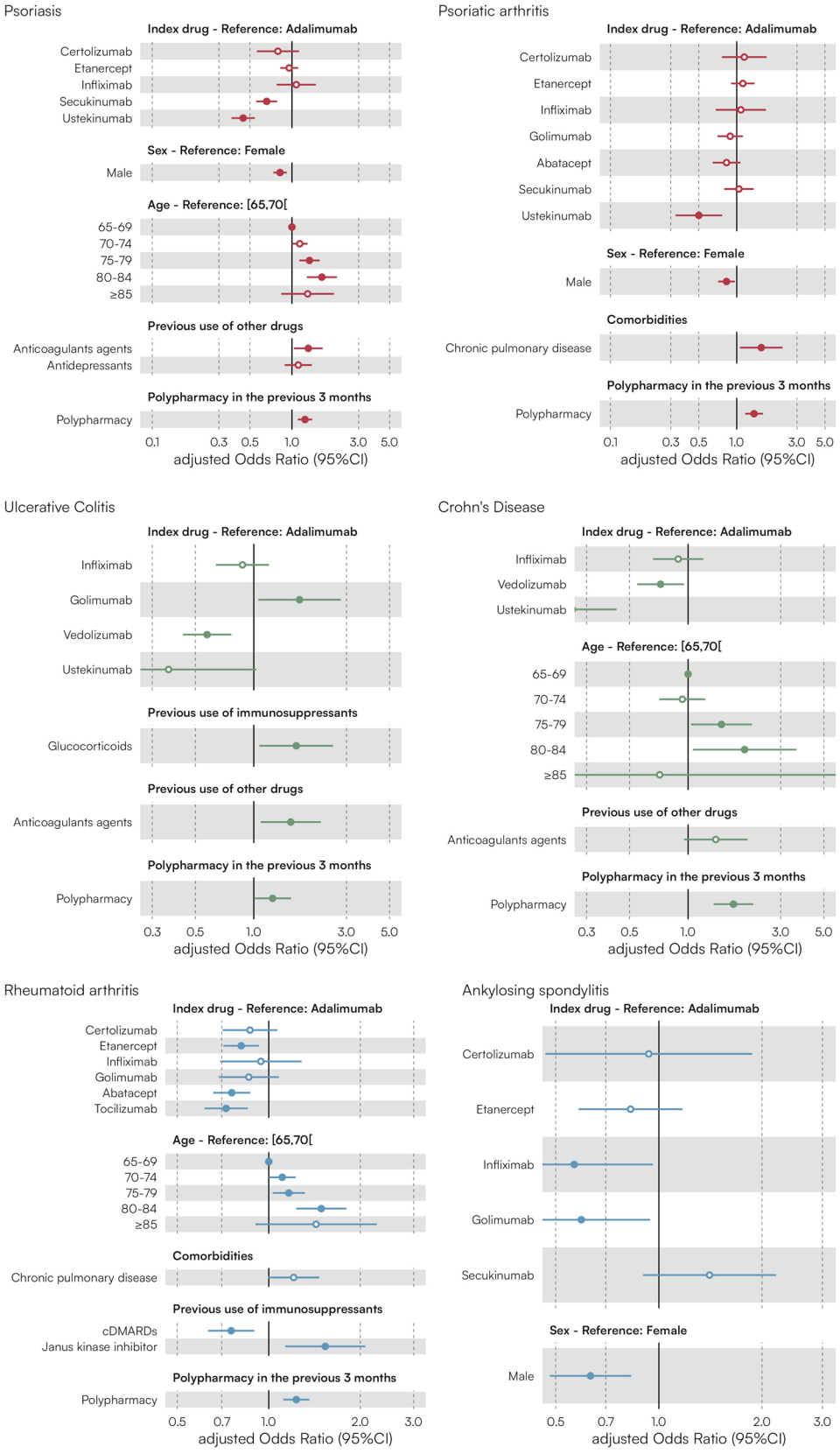

Fig. 5 Adjusted odds ratio of biological drug treatment discontinuation at 1 year, stratified by indication for use

health and quality of life [41, 42]. As expected, older age was also usually found as a predictive factor for discontinuation; older patients, who usually have worse baseline disease activity [43], may be more susceptible to adverse events, which may have resulted in high rates of nonpersistence. In older patients with IBDs receiving biological drugs, advanced age is associated with higher infection risk, and these patients have a threefold increased risk of developing infections compared with younger patients [5, 44]. However, it is crucial to additionally evaluate the efficacy of biologic drugs in older patients, as there is a lack of evidence supporting their benefit–risk profile in this population [45]. Without considering expected efficacy, weighing the risks and benefits of these therapies becomes difficult, especially in older populations where comorbidities and frailty may complicate treatment outcomes and choices. For instance, certain biological drugs are contraindicated in the presence of specific comorbidities, which are often more prevalent in older patients. For example, the use of infliximab is not recommended in patients with moderate-to-severe heart failure [46]. Therefore, therapeutic decisions must carefully consider the individual patient's overall health status and the potential for achieving meaningful clinical benefit.

Given that approximately 50% of older patients discontinue biological therapies within the first year, it is essential to focus on practical strategies to improve treatment outcomes for this population: (1) it is crucial to generate robust evidence that helps clinicians select the most suitable biological drug, considering the patient's individual characteristics to ensure optimal safety and efficacy; (2) clinicians must closely monitor older patients to identify and manage potential adverse effects and drug interactions that could lead to treatment discontinuation, and (3) a multidisciplinary approach involving specialists (rheumatologists, dermatologists, gastroenterologists, and geriatricians) is essential to address the complexity of managing multiple conditions in older patients with IMIDs.

Finally, we believe real-world evidence can play a pivotal role in evaluating biological drugs' effectiveness and safety profiles, as already mentioned in other observational studies [47–49]. In particular, our findings emphasize the importance of conducting large-scale studies using multiple distributed databases, as they provide a sufficiently large sample size to assess the safety and effectiveness of individual therapies in older patients. To generate stronger evidence, new study designs, such as clinical trial emulation, could be used to improve the quality of the available evidence. In addition, linking administrative data with other data sources could offer valuable information not captured in administrative datasets alone. Leveraging these approaches will be crucial in guiding clinical decision-making and informing future clinical guidelines for older populations.

4.1 Strengths and Limitations of the Study

This study has several strengths. First, we included a large cohort of patients (about 25,000 incident biological drug users with IMIDs) with an overall follow-up of 10 years. Secondly, the long-term study period allowed the description of the pattern of biological drug use over time and persistence to index biological drugs at 5 years of follow-up after the index date. Moreover, we considered all the biological drugs approved for IMIDs, thus not restricting the analysis to drugs approved for only one of these diseases, as done in previous studies. Finally, we explored the predictive factors of discontinuation of biological drugs, which have not been investigated so far in the older population.

Nevertheless, some limitations warrant caution. First, we found that about 16.3% of patients had a missing indication. Notably, within the anti-interleukin class, most of the missing indications (about 70%) were related to patients treated with tocilizumab. Tocilizumab is approved for RA and other indications such as giant cell arteritis and COVID-19. In particular, giant cell arthritis is a disease with an average age of onset of 70 years [50]. The developed META-algorithm used to distinguish by indications for the use of biological drugs in administrative data [8] did not track indications such as giant cell arthritis or COVID-19, thus explaining the higher proportion of tocilizumab patients without an indication. Despite its limitations, a previously published validation study reported high validity estimates in detecting RA, AS, CU, CD, and PsO/PsA in the VALORE distributed database network. Second, information such as disease severity was not available in administrative data, thus limiting the interpretation of our findings. Third, while DDDs were used to calculate treatment coverage, variations in dosage based on patient weight could not be fully excluded. However, for most indications, there is no clear indication of dosage changes for older patients compared with the general adult population in the biological drug product summary characteristics. As previously mentioned, in future observational studies, one approach to overcoming these limitations would be to link administrative data with additional sources, such as registries.

5 Conclusions

This large cohort study of approximately 25,000 older Italian patients with IMID documented a sixfold increase in the use of biological therapies from 2010 to 2022. Overall biological drug treatment persistence rate among patients ≥ 65 years old at 1 year was about 50%, with polypharmacy and more advanced age being associated with a higher risk of discontinuation. These findings highlight the importance

of carefully assessing the benefit–risk profile of biological therapies in older patients with IMIDs, particularly in those with polypharmacy. Close monitoring for adverse effects and potential drug–drug interactions also became crucial. Hence, large-scale cohort studies to investigate the benefit–risk profile of biological drugs in older patients in real-world setting are urgently needed for a more tailored treatment approach. Addressing these gaps is essential to optimize treatment strategies and improve clinical outcomes in this vulnerable population, especially considering the limited evidence coming from randomized clinical trials.

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Declarations

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Conflict of Interests G.T. participated in advisory boards and seminars as lecturer on topics not related to the paper and was sponsored by the following pharmaceutical companies in the last 2 years: Eli Lilly; Sanofi; Amgen; Novo Nordisk; Sobi; Gilead; Celgene; Daiichi Sankyo; Takeda; and MSD. He is also scientific coordinator of the pharmacoepidemiology team at the University of Verona and of the academic spin-off "INSPIRE S.r.l." that in the last 2 years carried out observational studies/systematic reviews on topics not related to the content of this article and which were funded by PTC Pharmaceutics, Kyowa Kirin, Shionogi, Shire, Chiesi, and Daiichi Sankyo. Y.I. is the CEO of the academic spin-off "INSPIRE S.r.l.," which has received funding for conducting observational studies from contract research organizations (RTI Health Solutions, Pharmo Institute N.V.) and from pharmaceutical companies (Chiesi Italia, Kyowa Kirin S.r.l., Daiichi Sankyo Italia S.p.A.).

Availability of Data And Material (Data Transparency) The datasets generated and/or analyzed during the current study are not publicly available because of privacy reasons. Requests to access the datasets should be directed and motivated to the corresponding author.

Code Availability (Software Application or Custom Code) Not applicable.

Author's Contributions F.S., A.S., G.C., and G.T. contributed to the writing of the article and methodology; G.P. and C.M., contributed to the conduction of the analysis; S.A.M.U and A.C. contributed to data interpretation; C.B., L.L., Y.I., O.L., M.Z., D.A., P.S., A.C., A.S., S.L., V.B., S.L., P.C., P.R., L.E., E.S., A.P., R.F.S., G.D.S., A.A., S.A.P, R.D.C., G.B., A.M.P.M, F.B., C.S., I.S., M.T., R.G., S.S.A., and M.M. contributed to data extraction and data interpretation. All the authors reviewed the final version of the article.

Ethics Approvals This study was conducted in the context of the multiregional active pharmacovigilance project called Post-marketing evaluation of the benefit–risk profile of originator biological drugs and biosimilars in the dermatological, rheumatological, gastroenterological and onco-hematological areas through the establishment of a single multiregional network for the integrated analysis of data from health databases, active surveillance and clinical registers—VALORE project, funded by the Italian Medicine Agency. The study protocol was registered in the HMA-EMA catalogue of real-world data sources and studies (EUPAS1000000211), and the ethical committees of the Academic Hospitals of Messina and Verona approved it.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

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