ORIGINAL ARTICLE

Safety of classic and biologic systemic therapies for the treatment of psoriasis in elderly: an observational study from national BIOBADADERM registry

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Abstract

Background Psoriasis patients over 65 years-old (elderly) constitute a growing group, underrepresented in clinical trials, and likely to be more prone to adverse events.

Objective To describe safety of systemic psoriasis therapy in patients over 65 years-old compared to younger patients.

Methods Patients registered in Biobadaderm, a Spanish national registry of psoriasis patients treated with systemic therapy, were grouped in elderly (≥ 65 years old) and younger patients. Rates of adverse events were described by severity and type, and the risks compared in both groups, taking into account exposure to classic or biologic drugs, using Cox regression.

Results 175 (9.8%) of 1793 patients were elderly. Overall risk of adverse events was not higher in elderly (drug group adjusted HR 1.09 (95%CI: 0.93-1.3)). Serious adverse events were more common in elderly (drug group adjusted HR 3.2 (95%CI: 2.0-5.1)). Age adjusted HR of all adverse events was lower for patients exposed to biologics compared to classic drugs in the whole sample (HR 0.7 (95%CI: 0.6-0.7)). Age did not seem to modify the effect of therapy (biologic vs. classic) in the risk of adverse events (likelihood ratio test for interaction, p = 0.12 for all adverse events, p = 0-09 for serious adverse events).

Conclusions Serious adverse events are more common in elderly patients, although they may be related to other variants that are associated with this age group and not due to the treatment itself. Use of biologics was associated with lower risk of adverse events in the whole group. We found no differences in this association between young and elderly. These results are reassuring, although uncontrolled confounding could not be excluded as an explanation for these findings, and the power of the study to detect differences was low.

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Conflicts of Interest

Dr Carretero served as a consultant and investigator for Abbott Laboratories, Janssen-Cilag Pty Limited, MSD and Pfizer Inc; and received grants form Abbott, Jannsen and Pfizer and equipment from MSD and Pfizer Inc.

Dr Ferrandiz served as a consultant and speaker for Abbott Laboratories, Janssen Pharmaceuticals Inc, Pfizer and

Almirall SA; as a speaker for Abbott Laboratories, Janssen Pharmaceuticals Inc and Almirall SA received honoraria from Abbott Laboratories, Almirall SA, Janssen Pharmaceuticals Inc and received grants from Abbott Laboratories.
Dr Daudén served as a consultant for Abbott Laboratories, Amgen, Astellas, Celgene, Centocor Ortho Biotech Inc, Galderma, Glaxo, Jannsenn-Cilag, Leo Pharma, MSD, Novartis and Pfizer Inc; received honoraria from Abbott Laboratories, Amgen, Celgene, Janssen-Cilag Pty Ltd, Leo Pharma, MSD, Novartis and Pfizer Inc; participated in speakers' bureaus for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD and Pfizer Inc; and received grants from Abbott Laboratories, Janssen Pharmaceuticals Inc and Pfizer Inc.
Dr Vanaclocha participated as speaker for Abbott Laboratories, Pfizer Inc, MSD and Janssen Pharmaceuticals Inc.
Dr Herrera-Ceballos served as a consultant and speaker for Abbott Laboratories, Janssen Pharmaceuticals Inc and Pfizer-Wyett.
Dr De la Cueva acted as a consultant for Janssen-Cilag, Abbott, MSD, Pfizer and Leo-Pharma.
Dr Belinchón acted as a consultant for Pfizer-Wyeth; Janssen Pharmaceuticals Inc, MSD, Almirall SA and Leo-Pharma, and as a speaker for Abbott-Abbvie, Pfizer-Wyeth, Janssen Pharmaceuticals Inc and MSD.
Dr Sánchez-Carazo acted as a consultant for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD and Pfizer-Wyeth.
Dr Alsina acted as a consultant for Abbott Laboratories and Merck/Schering-Plough.
Dr López-Estebaranz served as a consultant for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD and Pfizer-Wyeth and as a speaker for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD and Pfizer-Wyeth.
Dr Ferrán participated in advisory boards for MSD, Pfizer, Abbvie and Jannsen, as a speaker for MSD, Abbvie and Janssen, as investigator for MSD, Abbvie, Pfizer and Janssen.
Dr Carrascosa served as a consultant and speaker for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD and Pfizer-Wyeth.
Dr Argila served as Advisory Board member, consultant, grants, research support, participation in clinical trials, honorarium for speaking, research support, with the following pharmaceutical companies: Abbott, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, MSD-Schering-Plough, Celgene.
Dr Rivera participated in advisory boards for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD and Pfizer-Wyeth.
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This work was conducted within the group. The following members participated in acquisition of data and review of the manuscript: Beatriz Pérez Zafrilla PhD, BPharm (Unidad de Investigación, Fundación AEDV); Carlos Muñoz-Santos, MD (Hospital Clinic of Barcelona, Barcelona); Victoria Mendiola-Fernández, MD, Cristina Sánchez Roldán, MD (Hospital Universitario Virgen de la Victoria, Malaga); Diana Ruiz-Genao, MD, Begoña Echeverría, MD (Hospital Universitario Fundación Alcorcón, Madrid); José Bañuls Roca, PhD, Juan Francisco Silvestre Salvador,MD, Pilar Albarés Tendero PhD and Isabel Betlloch Mas MD (Hospital General Universitario de Alicante, Alicante); and Sagrario Galiano Mejías, MD (Hospital Universitario Infanta Leonor, Madrid, Spain).

Background
Psoriasis is a common inflammatory cutaneous disorder that affects 0.73–2.9% of individuals of all ages in Europe.[1,2] Traditional systemic therapies may control the expression of this disease although they are limited by potential organ toxicity. Biologic therapies have meant a change in the management of psoriatic patients, with a high rate of response and few short-term side-effects.[3]

Biobadaderm, founded in 2008, is a national drug registry of patients with psoriasis on any systemic therapy. The aim of this registry is to identify adverse events in long-term treatments with biologic or classic therapies, or after discontinuation of them, and estimate their incidence and predisposing risk factors.

The chronic course of psoriasis and the increase in life expectancy led to elderly constituting a significant group in psoriasis patients.[4]

Individuals older than 65 years old are usually excluded of different clinical trials and studies, so that there are few data of clinical features and toxicities in this group of patients.[5] Moreover, these patients may have more comorbidities and drug interactions that may produce a higher rate of adverse events. Registries may show a better approach to describing safety in clinical practice, including all the range of ages and without exclusion criteria.[6]

Our objective was to compare the safety profile of classic and biologic therapies in patients with psoriasis in elderly population and describe the features of this specific group of population that is often excluded of different clinical trials and studies.

Methods

Population

Data were obtained from the Biobadaderm database, the Spanish Registry of Adverse Events from Biological Therapy in psoriasis. It consists of a prospective inception cohort started in 2008, in which, for each patient receiving a new biologic therapy, another patient receiving a new traditional systemic drug, and who had not been treated with biologics before, is also included. A retrospective search of patients starting biologic therapy from 2005 to 2008, was also included initially in the study. Data included in analysis were all data available until October 2012.

Details about methodology and data collection have been previously described.[7] Biobadaderm has been approved by the Hospital 12 de Octubre Ethics Committee (Madrid, Spain), and all patients gave their written consent to participate.

Variables evaluated

Demographic data, comorbidities, previous treatments, risk factors and causes of treatment withdraws are included in the registry. All adverse events that were serious (according to the 'International Conference on Harmonisation E2A Guideline')[8] or lead to a change in therapy or to unexpected medical attention were included in the registry. A serious adverse event is defined as: 'any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect'.[8]

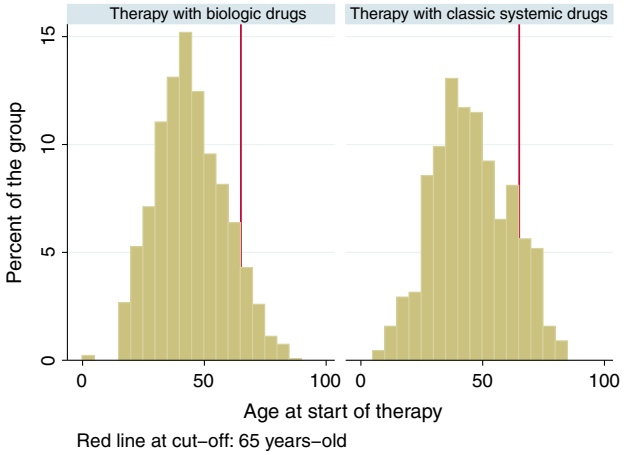

Figure 1 Age distribution of patients in Biobadaderm, grouped by therapeutic group (classic drugs vs. biologics).

Statistical analysis

Our study population was divided in two groups: <65 years old (yo) and 65 or more yo. We compared the incidence of different kinds of adverse events in these two groups, including patients treated with biologics and classic therapy. A descriptive analysis was performed, comparing both groups. Multivariate analysis consisted of Cox proportional hazards models analysing time to first event. All analyses were done using Stata 12 (Stata Corp., College Station, TX, USA, 2011).

Results

Descriptive analysis

A total of 175 elderly patients (over 65 years old) and 1618 controls were included in this study. Age distribution of Biobadaderm participants, likely to be representative of patients receiving systemic therapy in Spain, is shown in Fig. 1.

Patient characteristics are described in Table 1. Older patients included a higher percentage of females, had a longer length of disease and had similar PASI. Except for psoriatic arthritis, all comorbidities were more common in elderly patients. There were no large differences in the history of previous therapy between elderly and control group.

Distribution of treatments in the study is different in both groups (Table 2), as younger received more treatments with biologics (67.2% of total of younger patients against 50.3% in elderly). However, this has changed over the time, as the percentage of elderly, receiving biologic therapy has grown from 7.7% in 2008 to 11.73% in 2012. (trend test, $P = 0.047$), as well as, patients on classic therapies had decreased from 23.2% in 2008 to 9% in 2012 (trend test, $P < 0.01\%$).

Etanercept is the biologic more frequently used in both groups, whereas infliximab is the less common.

Table 1 Descriptive analysis of study population

	Classic therapy		Biologic therapy		Total	
	<65 yo	≥65 yo	<65 yo	≥65 yo	<65 yo	≥65 yo
N patients	735 (100%)	112 (100%)	883 (100%)	63 (100%)	1618 (100%)	17 5(100%)
Female, *n* (%)	306 (41.6%)	47 (42.0%)	319 (36.1%)	32 (50.8%)	625 (38%)	79 (45%)
Age, years old (SD)*	41.4 (12.7)	71.5 (4.8)	41.8 (11.3)	71.3 (5.0)	41.6 (12–0)	71.4 (4.9)
Length of disease, y (SD)†	14.0 (12.0)	21.2 (20.2)	17.8 (11.3)	23.0 (19.0)	16.1 (11.8)	21.9 (19.7)
PASI (SD)‡	10.8 (7.1)	9.9 (8.1)	16.2 (9.5)	19.4 (11.9)	13.8 (8.9)	13.4 (10.7)
Psoriasis subtype *n* (%)						
Plaque psoriasis	661 (89.9%)	106 (94.6%)	840 (95.1%)	55 (87.3%)	1501 (92.8%)	161 (92.0%)
Guttate psoriasis	43 (5.9%)	1 (0.9%)	41 (4.6%)	4 (6.4%)	84 (5.2%)	5 (2.9%)
Erythrodermic psoriasis	6 (0.8%)	6 (5.4%)	23 (2.6%)	5 (7.9%)	29 (1.8%)	11 (6.3%)
Pustular psoriasis	11 (1.5%)	1 (0.9%)	7 (0.8%)	4 (6.4%)	18 (1.1%)	5 (2.9%)
Palmoplantar pustulosis	40 (5.4%)	7 (6.3%)	8 (0.9%)	4 (6.4%)	48 (3.0%)	11 (6.3%)
Annular pustular psoriasis	0 (0%)	1 (0.9%)	5 (0.6%)	0 (0%)	5 (0.3%)	1 (0.6%)
Acrodermatitis Hallopeau	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)
Comorbidities *n* (%)						
Psoriatic arthritis	59 (8.0%)	9 (8.0%)	160 (18.1%)	13 (20.6%)	219 (13.5%)	22 (12.6%)
Ischaemic cardiomyopathy	20 (2.7%)	12 (10.7%)	15 (1.7%)	7 (11.1%)	35 (2.2%)	19 (10.9%)
Chronic heart failure	4 (0.5%)	7 (6.3%)	2 (0.2%)	5 (7.9%)	6 (0.4%)	12 (6.9%)
Hypertension	127 (17.3%)	70 (62.5%)	143 (16.2%)	41 (65.1%)	270 (16.7%)	111 (63.4%)
Diabetes	55 (7.5%)	42 (37.5%)	92 (10.4%)	22 (34.9%)	147 (9.1%)	64 (36.6%)
Hypercholesterolaemia	174 (23.7%)	52 (46.4%)	198 (22.4%)	31 (49.2%)	372 (23.0%)	83 (47.4%)
Chronic obstructive pulmonary disease	11 (1.5%)	12 (10.7%)	12 (1.4%)	8 (12.7%)	23 (1.4%)	20 (11.4%)
Chronic hepatopathy	8 (1.1%)	7 (6.3%)	61 (6.9%)	4 (6.4%)	85 (5.3%)	11 (6.3%)
Renal failure	8 (1.1%)	8 (7.1%)	7 (0.8%)	3 (4.8%)	15 (0.9%)	11 (6.3%)
Previous cancer	25 (3.4%)	19 (17.0%)	15 (1.7%)	2 (3.2%)	40 (2.5%)	21 (12.0%)
Cancer in the last 5 years (excluded non-melanoma skin cancer)	5 (0.7%)	6 (5.4%)	3 (0.3%)	1 (1.6%)	8 (0.5%)	7 (4.0%)
Lymphoma	1 (0.1%)	2 (1.8%)	6 (0.7%)	0 (0%)	7 (0.4%)	2 (1.1%)
Hepatitis B	29 (4.0%)	6 (5.4%)	31 (3.5%)	2 (3.2%)	60 (3.7%)	8 (4.6%)
Hepatitis C	11 (1.5%)	3 (2.7%)	20 (2.3%)	2 (3.2%)	31 (1.9%)	5 (2.9%)
HIV	10 (1.4%)	0 (0%)	9 (1.0%)	0 (0%)	19 (1.2%)	0 (0%)
Classic treatments previous to initiation of the registry, *n* (%)						
PUVA	99 (13.5%)	18 (16.1%)	316 (35.8%)	24 (38.1%)	415 (25.7%)	42 (24%)
NB-UVB	79 (10.8%)	19 (17.0%)	147 (16.7%)	9 (14.3%)	226 (14.0%)	28 (16.0%)
Broad-band-UVB	22 (3.0%)	6 (5.4%)	50 (5.7%)	2 (3.2%)	72 (4.5%)	8 (4.6%)
Methotrexate	94 (12.8%)	19 (17.0%)	499 (48.0%)	28 (44.4%)	593 (36.7%)	47 (26.9%)
Cyclosporine	82 (11.2%)	11 (9.8%)	424 (48.0%)	23 (36.5%)	506 (31.3%)	34 (19.4%)
Acitretin	92 (12.5%)	29 (25.9%)	277 (31.4%)	29 (46.0%)	369 (22.8%)	58 (33.1%)
Etretinate	9 (1.2%)	2 (1.8%)	36 (4.1%)	4 (6.4%)	45 (2.8%)	6 (3.4%)

% from each column.

*Age at the beginning of the treatment, years old (SD).

†Years from diagnosis of psoriasis until the beginning of the study: years (SD).

‡PASI: Psoriasis Area and Severity Index, at the beginning of the treatment (SD).

The main reason for treatment discontinuation in both groups (Table 3) is lack or loss of efficacy (43.5% in younger patients and 37.5% in elderly), followed by remission (21.9% and 23.9% respectively). Discontinuation for adverse event seems more frequent in elderly (18.2% in ≥65 yo and 12% in younger). Fisher's exact test is not significant, although statistical power of this test is low, and it cannot be discarded.

Risk ratio associated with age of the different types of adverse events by MedDRA classification in both groups of treatments is resumed in Table 4. As this leads to dividing the sample in many

Table 2 Distribution of treatments of our study population

Treatment	<65 yo *N* (%) *	≥65 yo *N* (%)	Total *N* (%)
Acitretin	205 (7.0%)	69 (21.3%)	274 (8.4%)
Cyclosporine	282 (9.7%)	19 (5.9%)	301 (9.3%)
Methotrexate	472 (16.2%)	73 (22.5%)	545 (16.8%)
Etanercept	658 (20.5%)	70 (18.8%)	728 (20.3%)
Infliximab	200 (6.2%)	9 (2.4%)	209 (5.8%)
Adalimumab	570 (17.8%)	30 (8.1%)	600 (16.8%)
Efalizumab	200 (6.2%)	19 (5.1%)	219 (6.1%)
Ustekinumab	334 (10.4%)	35 (9.4%)	369 (10.3%)
Total	2921 (100%)	324 (100%)	3245 (100%)

**N*: number of cycles of treatments during the study. % percentage of the column.

parts, none of the diagnostic groups is significantly associated with an increased risk in elderly. However, this test has low power for detecting such a difference. Severity of adverse events in each group is shown in table 5.

Multivariate analysis showed that elderly do not have a drug exposure-adjusted increased risk of overall adverse events [HR: 1.09 (IC95%: 0.9–1.3)]. However, serious adverse events are more common in this group of population [Adjusted HR: 3.2 (IC95%: 2.0–5.1)]. Use of biologics in the whole population compared to classic drugs is associated with an adjusted decreased risk of adverse events [HR 0.7 (95% CI: 0.6–0.7)], and a similar risk of serious adverse events) [HR 1.4 (95% CI: 0.9–2.3)]. We could not detect a difference between elderly and younger in these effects of exposure to biologics (Table 6).

A sensitivity analysis did not show changes when the small percentage of retrospective data (<10% of follow-up time) were excluded.

Discussion

Biologic agents have become an important tool in the management of psoriatic patients. However, efficacy and safety studies are scarce in elderly, a group of population that is usually excluded from clinical trials. Treatment of these patients has a variety of safety concerns, as they may present with other comorbidities, drug interactions and dose adjustments.[9]

Most of the studies have been performed with rheumatology patients,[10–14] and just a few of them in patients with psoriasis.[15]

Etanercept is the anti-TNF with more efficacy and safety studies.[10–12]

A systematic review about the efficacy and safety of anti-TNF in elderly with rheumatoid diseases showed that most of the studies agree with the similar efficacy and safety of these agents in older and younger patients.[16]

Only in a few studies of rheumatoid arthritis, TNF antagonists appear less effective in elderly compared with younger patients.[17,18]

In terms of safety profile, some studies have shown no significant differences in adverse events in elderly compared with younger patients.[12,13,19,20] However, other observational studies on rheumatoid diseases resulted in significantly higher number of adverse events in elderly compared with younger patients,[11] specially, for the increased risk for severe infections in elderly.[14] Causes of discontinuation of TNF antagonist have been studied, showing that older patients discontinue treatment more frequently as a result of an adverse event, whereas younger patients due to inefficacy.[21] Moreover, the diagnosis itself is another predictive factor for efficacy and safety, as patients with rheumatoid arthritis discontinued treatment more frequently due to inefficacy and adverse events, than patients with ankylosing spondyloarthritis do.[21] This fact supports that specific studies in psoriatic patients should be performed, as conclusions may differ from results in patients with rheumatoid diseases.

In the present study, we observed that the risk of any adverse event is lower in biologic treatment compared to classic, and the age of patients makes no differences in this statement. However, serious adverse events are increased in elderly, although this may be related to other comorbidities that are associated to this group of population, and not to the psoriasis treatment itself. No differences were found in the risk of adverse events in elderly associated with biologic exposure.

Table 3 Reasons for discontinuation of treatments

	<65 yo		≥65 yo	
	Withdrawals *N* (%)	% of initiated treatments	Withdrawals *N* (%)	% of initiated treatments
Inefficacy, Loss of efficacy	495 (43.5%)	25.2	33 (37.5%)	20.3
Adverse event	137 (12.0%)	7.0	16 (18.2%)	9.8
Pregnancy	25 (2.2%)	1.3	0 (0%)	0
Loss to follow-up	33 (2.9%)	1.7	0 (0%)	0
Remission	249 (21.9%)	12.7	21 (23.9%)	12.9
Other	200 (17.6%)	10.2	18 (20.5%)	11
Total	1139 (100%)	58.1	88 (100%)	54

Table 4 Incidence risk ratio of all adverse events between patients over 65 and under 65 years old

	Classic systemic Therapy IRR in elderly (95% CI)	Biologic Therapy IRR in elderly (95% CI)	Total IRR in elderly(95% CI)
Infections and infestations	1.01 (0.51–1.87)	1.21 (0.74–1.91)	1.23 (0.83–1.75)
Skin and subcutaneous tissue disorders	1.34 (0.45–3.30)	0.82 (0.10–3.06)	1.30 (0.55–2.64)
Musculoskeletal and connective tissue disorders	0.41 (0.10–1.23)	1.27 (0.49–2.77)	0.74 (0.36–1.40)
Investigations†	2.32 (0.61–6.23)	1.22 (0.32–3.27)	1.55 (0.66–3.15)
General disorders and administration site conditions	3.80 (0.43–15.51)	1.37 (0.36–3.72)	1.65 (0.59–3.77)
Hepatobiliary disorders	0.70 (0.24–1.72)	1.12 (0.30–3.04)	1.17 (0.54–2.27)
Nervous system disorders	0.23 (0.07–0.59)	1.45 (0.38–4–02)	0.77 (0.35–1.51)
Gastrointestinal disorders	1.09 (0.42–2.40)	0.90 (0.17–2.90)	1.03 (0.48–1.99)
Injury, poisoning and procedural complications	0.79 (0.14–2.86)	1.02 (0.12–4.17)	1.00 (0.30–2.56)
Metabolism and nutrition disorders	0.49 (0.18–1.14)	0.91 (0.18–2.86)	0.82 (0.38–1.60)
Neoplasms benign, malignant and unspecified	1.03 (0.28–3.22)	0.87 (0.22–2.48)	0.92 (0.39–1.93)
Surgical and medical procedures	0.82 (0.02–5.78)	1.79 (0.34–5.93)	1.44 (0.37–4.06)
Blood and lymphatic system disorders	1.11 (0.36–3.12)	0.66 (0.20–1.76)	0.83 (0.40–1.64)
Psychiatric disorders	2.11 (0.21–11.08)	0	2.57 (0.29–10.75)
Renal and urinary disorders	0.18 (0.00–1.49)	1.12 (0.13–4.69)	0.76 (0.15–2.49)
Respiratory, thoracic and mediastinal disorders	0.35 (0.32–2.44)	1.87 (0.20–8.80)	0.86 (0.21–2.75)
Vascular disorders	0.42 (0.10–1.27)	1.99 (0.49–6.05)	1.13 (0.45–2.46)
Eye disorders	0.87 (0.02–10.83)	0.48 (0.04–2.94)	0.51 (0.88–2.14)
Cardiac disorders	1.11 (0.36–3.12)	0.50 (0.11–1.73)	0.63 (0.22–1.67)
Reproductive system and breast disorders	1.21 (0.10–10.54)	0.68 (0.01–5.05)	1.28 (0.23–4.85)
Pregnancy, puerperium and perinatal conditions	–	–	–
Ear and labyrinth disorders	–	0.59 (0.12–5.31)	0.59 (0.12–5.31)
Congenital, familial and genetic disorders	–	–	–
Immune system disorders	–	5.55 (0.11–69.10)	5.55 (0.11–69.10)
Endocrine disorders	–	–	–
Social circumstances	–	–	–

†Term used by MeDRA to refer to alterations of tests and studies.

Table 5 Severity of adverse events

	<65 yo		≥65 yo	
	Classic systemic therapy	Biologic therapy	Classic systemic therapy	Biologic therapy
Serious	33 (3.78%)	105 (5.95%)	28 (13.73%)	20 (11.76%)
No serious	838 (96.10%)	1655 (93.82%)	174 (85.29%)	148 (87.06%)
Fatal	1 (0.11%)†	4 (0.23%)*	2 (0.98%)§	2 (1.18%)‡
Total	872 (100%)	1764 (100%)	204 (100%)	170 (100%)

*Fatal adverse events in <65 yo on biologic therapy: 2 cases of neoplasms, 1 psychiatric disorder and 1 vascular disorder.
†Fatal adverse events in <65 yo on classic therapy: 1 neoplasm.
‡Fatal adverse events in ≥65 yo on biologic therapy: 1 neoplasm, 1 General disorders and administration site conditions.
§Fatal adverse events in ≥65 yo on classic therapy: 1 neoplasm and 1 nervous system disorder.

Biologic therapies are initiated more often in younger, because of the existing fear of using them in elderly, in the absence of enough safety studies in this group of population.[13] During the course of the study, a tendency to use more biologic treatments in elderly, and fewer classic drugs was also observed.

Our study has some limitations, including the small simple size in elderly (175 patients, compared with 1618 younger patients) that leads to wide confidence intervals in the estimation of risks and risks ratios, and the lack of data about uncommon adverse events. Confusion by indication of treatment was also possible, as patients are usually selected to receive a specific

Table 6 Risk of adverse events in elderly compared to younger cohort

	All adverse events	Serious adverse events
Univariate analysis		
Incidence risk ratio in elderly against younger (95% CI)	1.2 (0.98–1.3)	**3.3 (2.0–5.3)**
Test for interaction of elderly and exposure to biologics*	Homogeneity test: $P = 0.19$	Homogeneity test: $P = 0.19$
Multivariate analysis (Cox model including exposure to biologics and elderly)		
Adjusted Hazard ratio of elderly against younger (95% CI)	1.09 (0.93–1.3)	**3.2 (2.0–5.1)**
Adjusted Hazard ratio of biologics vs. classic drugs (95% CI)	**0.7 (0.6–0.7)**	1.4 (0.9–2.3)
Test for interaction of elderly and exposure to biologics*	Likelihood ratio test for interaction term: $P = 0.12$	Likelihood ratio test for interaction term: $P = 0.09$

*Measures if the risk associated with exposure to biologics is different in elderly (vs. younger) patients.
Bold values indicate statistically significant results.

agent to minimize adverse events. As in all observational studies, it is also possible that the associations found were influenced by the effect of confounding variables that had not been measured.

In conclusion, rates of adverse events are not increased in elderly except for the rate of serious adverse events, although this may be related to other variants but therapies that are associated to this group of population. No differences were found in the risk of adverse events in elderly related to biologic exposure. We think that patient age should not be considered a limit in choosing the therapeutic option, in agreement with other studies.[13,22]

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