Journal of Crohn's and Colitis, 2022, **16**, 946–953
https://doi.org/10.1093/ecco-jcc/jjab213
Advance access publication 3 December 2021
Original Article

Risk of Immunomediated Adverse Events and Loss of Response to Infliximab in Elderly Patients with Inflammatory Bowel Disease: A Cohort Study of the ENEIDA Registry

Margalida Calafat,[a,b] Míriam Mañosa,[a,b] Elena Ricart,[b,c] Pilar Nos,[b,d] Eva Iglesias-Flores,[e] Isabel Vera,[f] Antonio López-Sanromán,[g] Jordi Guardiola,[h] Carlos Taxonera,[i] Miguel Mínguez,[j] M. Dolores Martín-Arranz,[k] Luisa de Castro,[l] Ruth de Francisco,[m] Montserrat Rivero,[n] Esther Garcia-Planella,[o] Xavier Calvet,[b,p] Santiago García-López,[q] Lucía Márquez,[r] Fernando Gomollón,[b,s] Jesús Barrio,[t] Maria Esteve,[b,u] Fernándo Muñoz,[v] Javier P. Gisbert,[b,w] Ana Gutiérrez,[b,x] Joaquín Hinojosa,[y] Federico Argüelles-Arias,[z] David Busquets,[aa] Luís Bujanda,[b,bb] José L Pérez-Calle,[cc] Beatriz Sicilia,[dd] Olga Merino,[ee] Pilar Martínez,[ff] Fernando Bermejo,[gg] Rufo Lorente,[hh] Manuel Barreiro-de Acosta,[ii] Cristina Rodríguez,[jj] Mariana Fe García-Sepulcre,[kk] David Monfort,[ll] Fiorella Cañete,[a,b] Eugeni Domènech[a,b]; on Behalf of the ENEIDA Study Group of GETECCU*

[a]H.U. Germans Trias i Pujol, Badalona, Spain
[b]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Madrid, Spain
[c]H. Clínic Barcelona, Barcelona; IDIBAPS, Barcelona, Spain
[d]H. Universitari La Fe, València, Spain
[e]H. Reina Sofía, Córdoba, Spain
[f]H.U. Puerta de Hierro Majadahonda, Madrid, Spain
[g]H.U. Ramón y Cajal, Madrid, Spain
[h]H.U. Bellvitge (L'Hospitalet de Llobregat), Spain
[i]H.U. Clínico San Carlos, Madrid; Instituto de investigación del Hospital Clínico San Carlos, Madrid, Spain
[j]H.U. Clínico de València, València; Universitat de València, València, Spain
[k]H.U. La Paz, Madrid, Spain
[l]Complexo H.U, de Vigo, Vigo, Spain
[m]H.U. Central de Asturias and Instituto de Investigación Biosanitaria del principado de Asturias (ISPA), Oviedo, Spain
[n]H.U. Marqués de Valdecilla, Santander; IDIVAL, Santander, Spain
[o]H.U. de la Santa Creu i Sant Pau, Barcelona, Spain
[p]H.U. Parc Taulí, Sabadell, Spain
[q]H.U. Miguel Servet, Zaragoza, Spain
[r]Servei de Digestiu, Hospital del Mar, Barcelona and IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
[s]H. Clínico Lozano Blesa, Zaragoza; Instituto de Investigaciones Sanitarias de Aragón.
[t]Servicio de Gastroenterología. Hospital Universitario Río Hortega. Gerencia Regional de Salud de Castilla y León (SACYL), Valladolid, Spain
[u]H. Universitari Mútua Terrassa, Terrassa, Spain
[v]H.U.Salamanca, Salamanca, Spain
[w]H. U. de la Princesa, Madrid; Instituto de Investigación Sanitaria Princesa (IIS-IP), Universidad Autónoma de Madrid (UAM).
[x]H.G.U.Alicante, Alicante; Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL) , Spain
[y]Hospital Vithas 9 de Octubre, València, Spain
[z]Servicio de Digestivo, Hospital Universitario Virgen Macarena, Sevilla; Profesor Facultad Medicina de la Universidad de Sevilla, Sevilla, Spain
[aa]H. U. Girona Dr. J. Trueta, Girona, Spain
[bb]Instituto Biodonostia, Universidad del País Vasco (UPV/EHU), San Sebastián, Spain
[cc]H.U. Fundación de Alcorcón, Alcorcón, Spain
[dd]Hospital Universitario de Burgos, Burgos, Spain
[ee]H. de Cruces, Barakaldo, Spain
[ff]H. 12 de Octubre, Madrid, Spain
[gg]Hospital Universitario de Fuenlabrada and Instituto de Investigación Sanitaria del Hospital La Paz (IdiPAZ), Madrid, Spain
[hh]H.General de Ciudad Real, Ciudad Real, Spain

Received: August 17, 2021. **Revised:** October 19, 2021. **Accepted:** December 1, 2021

[ii]C.H.U. Clínico Santiago, Santiago de Compostela, Spain
[ii]C.H. de Navarra, Pamplona, Spain
[kk]H.G. Elche, Elche, Spain
[ll]Consorci Sanitari de Terrassa, Terrassa, Spain

*A complete list of the affiliations of the ENEIDA-GETECCU investigators is provided in the Appendix.
Corresponding author: Eugeni Domènech, MD, PhD, Gastroenterology & Hepatology Department, Hospital Universitari Germans Trias i Pujol, Carretera del Canyet s/n, 08916 Badalona, Catalonia, Spain. Tel: +34 93 497 8909; Email: eugenidomenech@gmail.com

Abstract

Background and Aims: Immunomediated adverse events [IAEs] are the most frequently reported infliximab [IFX]-related adverse events. Combination therapy may reduce their incidence, although this strategy is not recommended in elderly patients. We aimed to compare the rates of IFX-related IAEs and loss of response [LOR] in elderly and younger patients.

Methods: Adult patients in the ENEIDA registry who had received a first course of IFX therapy were identified and grouped into two cohorts regarding age at the beginning of treatment [over 60 years and between 18 and 50 years]. The rates of IAEs and LOR were compared.

Results: In total, 939 patients [12%] who started IFX over 60 years of age and 6844 [88%] below 50 years of age were included. Elderly patients presented a higher proportion of AEs related to IFX [23.2% vs 19%; $p = 0.002$], infections [7.1% vs 4.3%; $p < 0.001$] and neoplasms [2.2% vs 0.5%; $p < 0.001$]. In contrast, the rates of IAEs [14.8% vs 14.8%; $p = 0.999$], infusion reactions [8.1% vs 8.1%; $p = 0.989$], late hypersensitivity [1.3% vs 1.2%; $p = 0.895$], paradoxical psoriasis [1% vs 1.5%; $p = 0.187$] and drug-induced lupus erythematosus [0.6% vs 0.7%; $p = 0.947$] were similar in elderly and younger patients. LOR rates were also similar between the two groups [20.5% vs 19.3%; $p = 0.438$]. In the logistic regression analysis, IFX monotherapy, extraintestinal manifestations and female gender were the only risk factors for IAEs, whereas IFX monotherapy, extraintestinal manifestations and Crohn's disease were risk factors for LOR.

Conclusions: Elderly patients with inflammatory bowel disease have a similar risk of developing IFX-related IAEs and LOR to that of younger patients.

Key Words: Elderly; inflammatory bowel disease; adverse events.

1. Introduction

Inflammatory bowel disease [IBD], a chronic condition that includes ulcerative colitis [UC] and Crohn's disease [CD], typically develops in young adults and adolescents.[1] However, the prevalence of elderly patients with IBD is increasing due to both elderly-onset disease and long-lasting IBD.[2,3] Ageing is associated with an increase in comorbidities and, as a consequence, in polypharmacy and the risk of developing drug-related adverse events [AEs] due to errors in medication intake and drug interactions.[4–6] Ageing also implies certain physiological changes that may modify the pharmacokinetics and pharmacodynamics of drugs.[7] Moreover, elderly patients with IBD are clinically challenging since the relevance of safety issues and ultimate therapeutic goals may vary from those pursued in younger patients.

Furthermore, the elderly may present disturbances in their immune response. On the one hand, the so-called inflammaging phenomenon,[8] a chronic inflammatory state leading to an increased incidence of certain inflammation-related conditions [i.e. arthritis, cardiovascular events, autoimmune diseases], has been described. On the other hand, immunosenescence [the decline of the immune system associated with ageing][9,10] may also play a role in a number of immune responses, and has been suggested to explain the less aggressive phenotype of elderly-onset IBD.

Infliximab [IFX] was the first biological drug to be licensed for IBD. Its high clinical efficacy and the decrease in its cost due to the development of biosimilars have placed it as the first-line therapy for complicated IBD. The most common IFX-related AEs are immune-mediated [IAEs]. Although their definition is not well established, IAEs usually include acute infusion reactions [IRs], which represent between 5% and 20% of anti-tumour necrosis factor [anti-TNF]-related AEs[11,12] and could be related to antibodies to IFX [ATI] production,[13] autoimmune reactions that are associated with autoantibody formation (e.g. drug-induced lupus erythematosus [DILE]) and certain dermatological reactions such as paradoxical psoriasis or eczema.[14] Moreover, 23–46% of IBD patients who start anti-TNF therapy lose initial response to the drug (a phenomenon known as loss of response [LOR]) within the first year of treatment.[15,16] Although a standard definition, diagnostic criteria and pathogenesis for LOR are still lacking, most authors agree that immunogenicity plays a role in at least some cases since ATI have been associated with an increased risk of LOR.[13,17,18]

ATI production is decreased by the concomitant use of immunosuppressants with IFX. However, the increased risk of thiopurine-related AEs in the elderly IBD population[19–21] is well established. In contrast, in a previous study, we observed a lower rate of IRs with IFX among elderly-onset IBD patients.[3] Since combination therapy with IFX and immunosuppressants is usually advised to increase treatment persistence, IFX monotherapy might be a better option for elderly patients if a lower risk of IAEs and LOR is demonstrated, to avoid the increase in the risk of infections and neoplasms that has been observed in the elderly with combination therapy.[19,20] In contrast, data supporting the use of combination therapy with adalimumab [and also golimumab] are less robust and these drugs are more frequently prescribed as monotherapy. For this reason, assessing the need for combination therapy with these subcutaneous anti-TNF agents seems less necessary. Therefore, we aimed to assess the prevalence of IAEs and LOR in elderly IBD patients and young adults with IBD treated with IFX as the first biological therapy.

2. Methods

This is an observational, retrospective, multicentre, nationwide study promoted by the Spanish Working Group in IBD [GETECCU].

2.1. ENEIDA Registry

Patients were identified from the ENEIDA registry, a prospectively maintained database with continuous external monitoring to ensure the completeness and consistency of the data entered.[22] The registry was approved by the Ethics

Committees of each participating centre and patients signed an informed consent form. At the time of data extraction, the registry included more than 52 000 patients from 61 centres. The study was approved by the GETECCU Research Board. Clinical data, use, effectiveness and the AEs related to biological drugs were prospectively collected in the database.

2.2. Patients

All adult IBD patients to whom at least one dose of IFX had been administered as the first biological treatment for IBD were identified from the ENEIDA registry. Patients who had been treated with other biological drugs as the first biological agent [adalimumab, golimumab, ustekinumab or vedolizumab] were excluded. In those patients receiving several IFX treatment courses, only the first one was included for analysis.

Patients were grouped according to age at the beginning of IFX treatment. The *elderly* group included patients who started IFX over 60 years of age, whereas the *control* group included young adult patients who started IFX between 18 and 50 years of age. To avoid overlap between the study groups, follow-up was limited to 10 years and patients who started IFX between 51 and 59 years of age were excluded.

2.3. Variables and definitions

Data collection included age at the beginning of IFX, gender, IBD type, familial history of IBD, extra-intestinal manifestations and phenotypic IBD features. Regarding IFX treatment, we recorded the type of IAE as collected in the ENEIDA registry: acute IRs, delayed hypersensitivity, paradoxical psoriasis and DILE. In addition, LOR [clinical worsening after initial clinical improvement] was also recorded. As a consequence of the lack of a standard definition for these IAEs, they were registered at the discretion of each investigator in the registry. The use of concomitant immunosuppressants was also recorded. The follow-up period was the time interval between the beginning of IFX therapy and treatment discontinuation or the last follow-up visit, whichever occurred first. The main outcomes of the study were the development of IAEs [including acute IRs, delayed hypersensitivity, paradoxical psoriasis and DILE] and LOR.

2.4. Statistical analysis

Continuous variables are expressed as mean with standard deviation or median and interquartile range [IQR] as needed, and were compared using Student's *t* test. Categorical variables are expressed as proportions with a 95% confidence interval [CI] and compared with the Chi-square test. Logistic regression analyses were performed to investigate the potential risk factors for developing IAEs and LOR.

3. Results

Of the more than 52 000 patients included in the ENEIDA registry at the time of data extraction, 14 518 patients [28%] had been treated with biological agents. Of those, 7783 [15%] had been treated with IFX as the first biological treatment [Figure 1]. We included 939 [12%] patients who started IFX over 60 years of age and 6844 [88%] adult patients who started IFX below 50 years of age, between May 1998 and September 2018. Although gender was evenly distributed in the two groups, a lower proportion of CD, familial history of IBD, perianal disease, extraintestinal manifestations and concomitant use of immunosuppressants (but with a significantly greater use of MTX [4.9% vs 2.7%, $p < 0.001$]) was observed in the elderly group [Table 1].

Overall, elderly patients presented a significantly higher proportion of AEs related to IFX as compared to the control group [23.2% vs 19%; $p = 0.002$], as well as a significantly higher rate of infections [7.1% vs 4.3%; $p < 0.001$] and neoplasms [2.2% vs 0.5%; $p < 0.001$]. The IFX-related incidence rate of AEs in the elderly group was 12.96 per 100 patient-years and in the control group was 8.67 per 100 patients-years.

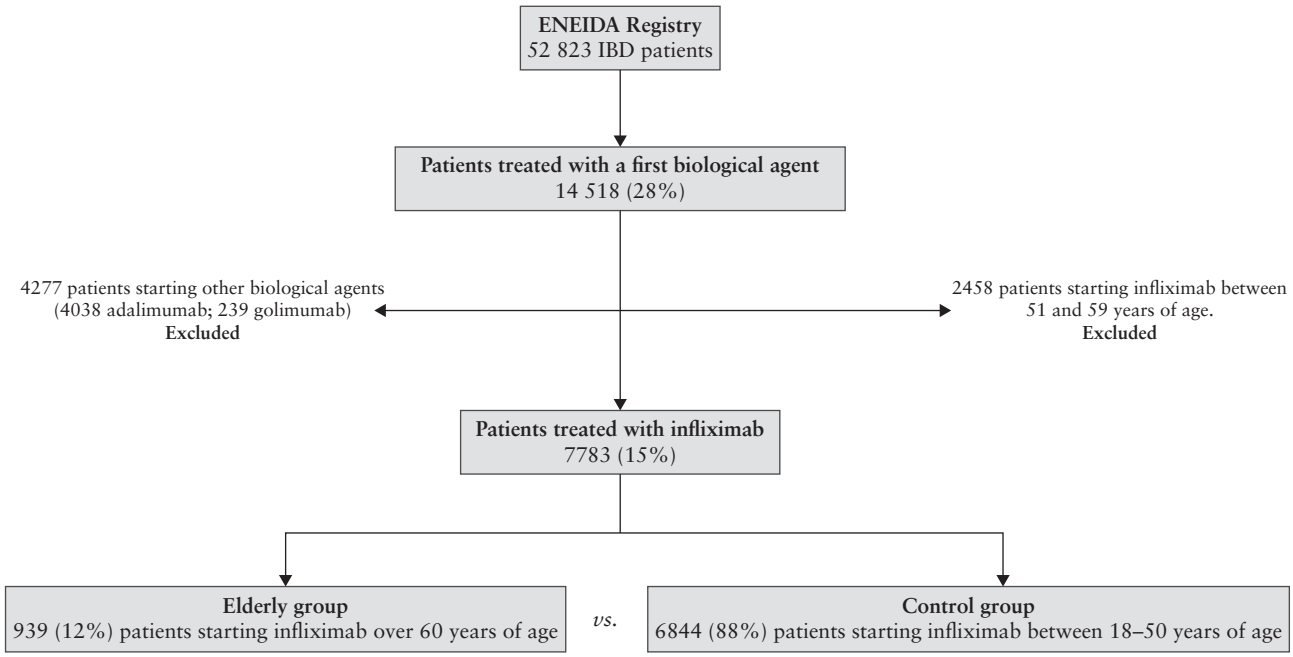

Figure 1. Study flow-chart.

3.1. IAEs and LOR

No differences in the overall rate of IAEs [14.8% elderly vs 14.8% control group; $p = 0.999$] and the rate of treatment discontinuation due to IAEs [12.1% elderly vs 11.4% control group; $p = 0.477$] were observed between study groups. The prevalence of the different type of IAE are summarized in Table 2. The incidence rate of IAEs was 8.26 per 100 patient-years in the elderly group and 6.76 per 100 patient-years in the control group. Again, no differences were observed according to the type of IAE between the elderly and control groups: acute IRs, late hypersensitivity, paradoxical psoriasis and DILE. Finally, the incidence rates of LOR were of 8.70 and 7.19 per 100 patient-years in elderly and control groups, respectively. No differences between the two study groups regarding LOR [20.5% elderly vs 19.3% control group; $p = 0.438$] were found.

3.2. Risk factors for IAEs and LOR

In the logistic regression analysis, IFX monotherapy (odds ratio [OR] 1.36; 95% CI 1.17–1.58; $p < 0.001$), extraintestinal manifestations [OR 1.47; 95% CI 1.26–1.72; $p < 0.001$] and female gender [OR 1.69; 95% CI 1.45–1.97; $p < 0.0001$] were the only risk factors identified for the development of IAEs [Table 3]. In addition, IFX monotherapy [OR 1.19; 95% CI 1.03–1.38; $p = 0.017$], extra-intestinal manifestations [OR 1.35; 95% CI 1.16–1.58; $p < 0.0001$] and CD [OR 1.23; 95% CI 1.04–1.45; $p = 0.015$] were identified as risk factors for developing LOR [Table 4]. Neither older age nor elderly-onset IBD were associated with the development of IAEs or LOR. No risk factors were observed when this analysis was performed only in the elderly group.

Since the proportion of patients using concomitant immunosuppressants was significantly higher in the control group [57% vs 48%; $p < 0.001$], we decided to perform a subanalysis excluding patients on combination therapy. In this subset of patients, extra-intestinal manifestations [OR 1.36; 95% CI 1.09–1.69; $p = 0.006$] and female gender [OR 1.93; 95% CI 1.56–2.41; $p < 0.001$] remained as risk factors for developing IAEs, whereas CD was a protective factor [OR 0.77; 95% CI 0.60–0.99; $p = 0.043$]. No risk factor was identified for LOR.

4. Discussion

Clinical experience gathered over more than 20 years of IFX use led to the implementation of certain measures to increase the efficacy and safety of the drug. Moreover, the licensing of anti-TNF biosimilars reinforced the positioning of these drugs in the first line of biological therapies in IBD. However, the elderly population is scarcely represented in pivotal clinical trials and data from elderly patients are rarely analysed separately in adult cohorts in real-world clinical studies. Therefore, it is unknown if all the measures applied to optimize IFX treatment are useful or even necessary in the elderly population. The optimal use of biological drugs in the elderly remains an unmet need in IBD. In fact, biological agents and immunosuppressants are used less often in elderly IBD patients than in young adults due not only to a less aggressive disease but also because of the fears of physicians regarding the development of AEs.[3,23]

To our knowledge, this is one of the largest cohorts assessing IFX-related IAEs in elderly patients. We observed that the

Table 1. Baseline clinical characteristics of the cohort. Data are expressed as raw numbers [frequency] or median [interquartile range]

	Elderly group [$n = 939$]	Control group [$n = 6844$]	p
Female gender	442 [47.1]	3325 [48.6]	n.s.
Age [years]	66 [62–71]	34 [27–41]	<0.05
IBD type			
Crohn's disease	536 [57.1]	4783 [69.9]	<0.05
Ulcerative colitis	392[41.7]	2000 [29.2]	
IBD unclassified	11 [1.2]	61 [0.9]	
Familial history of IBD	163 [12.6]	971 [16.1]	0.010
Perianal disease	180 [19.2]	2247 [32.8]	<0.05
Extra-intestinal manifestations	217 [23.1]	2131 [31.1]	<0.001
Concomitant immunosuppressants	337 [48.1]	3196 [57.0]	<0.001
Follow-up period, months [IQR]	11 [3–30]	14 [3–44]	<0.001
Elderly-onset IBD/Long-lasting IBD	512 [54.5]/427 [45.5]	—	—

Table 2. Prevalence of immunomediated adverse events and loss of response related to infliximab

Adverse events, *n* [%]	Whole cohort	Elderly group	Control group	p
Immunomediated adverse events	1153 [14.8]	139 [14.8]	1014 [14.8]	0.992
Treatment withdrawal due to IAEs	891 [11.4]	114 [12.1]	777 [11.4]	0.477
Drug-induced lupus erythematous	51 [0.7]	6 [0.6]	45 [0.7]	0.947
Acute infusion reactions	629 [8.1]	76 [8.1]	553 [8.1]	0.989
Late hypersensitivity	96 [1.2]	12 [1.3]	84 [1.2]	0.895
Paradoxical psoriasis	112 [1.4]	9 [1]	103 [1.5]	0.187

Table 3. Logistic regression analysis for risk factors of immunomediated adverse events in the total cohort and in those patients receiving infliximab in monotherapy

Immunomediated adverse events	Whole cohort [n = 7783]			Infliximab monotherapy[n = 2771]		
	OR	95% CI	p	OR	95% CI	p
Female gender	1.69	1.45–1.97	<0.001	1.93	1.56–2.41	<0.001
Extra-intestinal manifestations	1.47	1.26–1.72	<0.001	1.36	1.09–1.69	0.006
Infliximab monotherapy	1.36	1.17–1.58	<0.001	–	–	–
Elderly patients	–	–	0.866	–	–	0.837
Crohn's disease	–	–	0.085	0.77	0.60–0.99	0.043
Perianal disease	–	–	0.405	–	–	0.418
Familial IBD	–	–	0.800	–	–	0.434
Elderly onset of IBD	–	–	0.218	–	–	0.443

Table 4. Logistic regression analysis for risk factors of loss of response in the total cohort and in those patients receiving infliximab in monotherapy

Loss of response	Whole cohort [n = 7783]			Infliximab monotherapy [n = 2771]		
	OR	95% CI	p	OR	95% CI	p
Female gender	–	–	0.791	–	–	0.985
Extra-intestinal manifestations	1.35	1.16–1.58	<0.001	–	–	0.091
Infliximab monotherapy	1.19	1.03–1.38	0.017	–	–	
Elderly patients	–	–	0.924	–	–	0.919
Crohn's disease	1.23	1.04–1.45	0.015	–	–	0.307
Perianal disease	–	–	0.891	–	–	0.809
Familial IBD	–	–	0.991	–	–	0.524
Elderly onset of IBD	–	–	0.420	–	–	0.358

risk of IAEs was similar in elderly and younger IBD patients. Although our results might be biased by a less frequent use of concomitant immunosuppressants in elderly patients, the results remained the same when only those patients on IFX monotherapy were included in the analysis. Unfortunately, in one of the few studies focused on the incidence of anti-TNF-related AEs among elderly IBD patients, data on IAEs were not provided.[24] Of note, we also observed that female gender and extra-intestinal manifestations are risk factors for IAEs. Females are presumed to have an enhanced immunoreactivity as compared to males, leading to an increased risk of multiple autoimmune disorders and ATI development.[25–27] Similarly, extra-intestinal manifestations may be related to a higher immunogenicity[28] and have been associated with a more systemic involvement of IBD.

In a retrospective study led by our group in which treatment requirements in elderly-onset IBD were assessed as compared to young adults, we found that elderly patients presented IRs to IFX in a significantly lower proportion, but this was not the case for delayed hypersensitivity reactions and anaphylaxis.[3] Because of the small sample size in this previous study, we decided to perform a larger-sized study specifically designed to assess IAE prevalence in older patients. IRs are among the most common adverse events related to IFX treatment. In our cohort the prevalence of IRs was 8.1%, a figure within previously reported ranges.[14,29] In line with our results, no differences were observed regarding IRs in an Italian study including 114 elderly IBD patients.[30] In contrast, in a retrospective Belgian study with a small sample size, Lobatón *et al*. observed that IRs were less frequent in the elderly [4% vs 17%], although AEs were among the main reasons for stopping anti-TNF in those over 65 years of age.[31] Although the specific pathogenesis of IRs is still not fully understood in some cases, ATI production has been repeatedly involved[17,18] and the presence of ATI was associated with a two-fold increase in the risk of IRs in a recent meta-analysis.[13] In contrast, Paul and Roblin found that the risk of ATI formation was independently related to age over 60 years and IFX monotherapy in a small prospective cohort.[32] A possible explanation for this higher ATI incidence without an increased prevalence of IRs might be the consequence of an increased production [related to so-called inflammaging] of ineffective [related to immunosenescence] autoantibodies. In fact, elderly age was not a risk factor for IAEs or LOR even when we analysed only those patients on monotherapy.

The prevention of LOR remains one of the most important arguments for the use of combination therapy. However, when possible, combination therapy should be avoided in older patients for safety reasons. Moreover, the use of combination therapy was associated with a higher risk of treatment discontinuation.[33,34] Interestingly, we did not observe differences between elderly and younger patients regarding LOR. The overall prevalence of LOR in the whole cohort was 20%, a figure similar to that previously reported in the literature.[15,16] Data on LOR among elderly patients are scarce and mostly extrapolated from treatment discontinuation [which may not be synonymous with LOR]. In the above-mentioned Italian study, the prevalence of LOR in anti-TNF naïve elderly patients was significantly higher than in younger patients [29% vs 6%; $p < 0.001$].[30] In contrast, treatment discontinuation due to LOR in the Belgian study was lower in elderly patients [10% vs 42%].[31] Therefore, from our point of view,

the risk of LOR to IFX is not decreased with age, and combination therapy seems reasonable even in elderly patients.

Beyond the strength of being the largest study ever reported assessing IFX-related IAEs in an elderly IBD population, the present study has some limitations. First, and as a consequence of its retrospective design, there may be an under-reporting bias against mild IAEs. Second, IAE categorization was made at the discretion of the treating physician, due to the lack of a standard definition of IAEs; however, this would impact evenly in the two study groups. Finally, neither IFX trough levels nor ATI nor premedication treatment, as well as some other parameters that may impact on the pharmacokinetics of IFX [body mass index, serum albumin, IFX dosing, use of pre-medication], are collected in the ENEIDA registry; their availability would have strengthened our results in terms of treatment-related immunogenicity.

In conclusion, elderly IBD patients who start treatment with IFX have a similar risk of developing IAEs and LOR as younger patients, regardless of the use of concomitant immunosuppressants. Therefore, elderly patients may benefit from combination therapy to the same degree as younger patients. From this perspective, it seems reasonable to use combination therapy when using IFX in elderly patients, switching to monotherapy once the therapeutic effect is achieved to avoid safety concerns [mainly infections and malignancies] in the mid- and long term.

Funding

The ENEIDA registry of GETECCU is supported by AbbVie, Galápagos, Janssen, Biogen, Takeda and Pfizer.

Conflict of Interest

MC has served as a speaker, or has received research or education funding or advisory fees from Takeda, Janssen, Faes Farma, Gilead, Pfizer and MSD. MM has served as a speaker, or has received research or education funding or advisory fees from FAES, Ferring MSD, AbbVie, Takeda and Janssen. MM has served as a speaker or has received research or education funding or advisory fees from MSD, AbbVie, Pfizer, Takeda, Janssen, Faes Farma, Shire Pharmaceuticals and Almirall. ER has provided scientific advice/participated in medical meetings/received research funding from/received payment for presentations and advice from: MSD, Schering-Plough, Ferring, AbbVie, Takeda, Janssen, Fresenius Kabi and Pfizer. PN has served as speaker, consultant and advisory board of has received research funding from MSD, AbbVie, Janssen, Takeda, Roche, Sandoz, Ferring, Adacyte, Faes Farma, Kern Pharma, Pfizer, Vifor Pharma, Chiesi and Tillotts Pharma. IV has served as speaker, consultant and advisory member for and has received funding from: MSD, Abbvie, Pfizer, Ferring, Shire Pharmaceuticals, Takeda, Jannsen, Tillotts and Galapagos. ALSR has lectured for AbbVie, Pfizer, MSD and Janssen and has received research grants from AbbVie, MSD and Janssen/. JG has served as a speaker, or has received research or education funding or advisory fees from Roche, MSD, AbbVie, Kern Pharma, Takeda, Janssen, Pfizer, Ferring and GE Healthcare. CT has served as a speaker, a consultant and advisory member for MSD, AbbVie, Hospira, Pfizer, Takeda, Janssen, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Gebro Pharma and Tillotts. MR has served as a speaker, a consultant and advisory member for Merck Sharp and Dohme, AbbVie, Pfizer, Takeda and Janssen. EGP has served as a speaker or has received research or education funding or advisory fees from Ferring, Faes, Shire, Falk, AbbVie, MSD, Takeda, Pfizer and Jansen. XC has received grants for research from Abott, MSD and VIFOR, fees for advisory boards from Abott, MSD, Takeda, Pfizer, Janssen and VIFOR, and has given lectures for Abbott, MSD, Janssen, Pfizer, Takeda, Shire and Allergan. SGL has served as a speaker, consultant and advisory member or has received education or research funding from AbbVie, Janssen, MSD, Pfizer and Takeda. LM has served as a speaker, or has received research or education funding or advisory fees from MSD, AbbVie, Pfizer, Takeda and Janssen. FG has served as speaker for Janssen, AbbVie, Takeda, MSD and Pfizer. His group has received research funding from AbbVie, MSD, Janssen, Takeda and Pfizer. JB has served as speaker, as consultant or has received research or education funding from MSD, AbbVie, Takeda, Janssen and Ferring. FM has served as a speaker and has received research and educational funding and advisory fees from Janssen, AbbVie, Takeda and Pfizer. JPG has served as speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene, Gilead/Galapagos, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical and Vifor Pharma. AG has served as speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Pfizer, Kern Pharma, Takeda, Janssen, Ferring, Faes Farma, Shire Pharmaceuticals, Tillotts Pharma, Chiesi and Otsuka Pharmaceutical. JH has served as speaker, consultant and advisory member for or has received research funding from MSD, Abbvie, Ferring, Faes Farma, Shire Pharmaceuticals, Chiesi, Otsuka Pharmaceutical, USB Pharma and Dr. Falk Pharma. FA-A has served as speaker, consultant and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Takeda, Janssen, Ferring, Faes Farma, Shire Pharmaceuticals, Tillotts Pharma, Chiesi and Dr. Falk. DB has served as a speaker, or has received research or education funding or advisory fees from Ferring, AbbVie, Takeda, Janssen, Fresenius, Chiesi and Pfizer. JLP has served as speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Pfizer, Takeda, Janssen, Ferring, Faes Farma, Dr. Falk Pharma and Chiesi. FB has served as a speaker, a consultant and advisory member for or has received research funding from MSD, AbbVie, Takeda, Janssen, Pfizer, Biogen, Amgen, Ferring, Faes Farma, Tillotts Pharma, Falk Pharma, Chiesi, Gebro Pharma and Vifor Pharma. RL has served as a speaker, or has received research or education funding from MSD, AbbVie, Pfizer, Takeda, Janssen and Dr. Falk. MBA has served as a speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Janssen, Kern Pharma, Celltrion, Takeda, Gillead, Celgene, Pfizer, Sandoz, Biogen, Fresenius, Ferring, Faes Farma, Dr. Falk Pharma, Chiesi, Gebro Pharma, Roche, Adacyte and Vifor Pharma. CR has served as a speaker, or has received research or education funding or advisory fees from AbbVie, MSD, Takeda, Janssen, MSD, Tillotts and Pfizer. MFGS has served as speaker or has received research funding from MSD, AbbVie, Pfizer and Janssen. MSA has served as speaker, advisory member or has received research funding from AbbVie, Takeda, MSD, Janssen, Pfizer, Ferring, Chiesi and Falk. MNL has served as a speaker, or has received research or education funding from

AbbVie, MSD, Janssen, Pfizer, Takeda, Dr. Falk Pharma and Tillotts. LIFS has received education funding from Janssen, Tillotts and Salvat. MMH has served as speaker, consultant and advisory member for or has received research funding from Almirall, MSD, AbbVie, Takeda, Janssen, Ferring, Vifor Pharma and Fresenius. CMV has served as speaker and received consulting fees from AbbVie and Janssen. JMH has participated in educational activities, research projects, scientific meetings or advisory boards sponsored by Merck Sharp Dohme [MSD], Ferring, AbbVie, Janssen, Biogen, Sandoz, Kern Pharma, Faes Farma, Vifor Pharma and Takeda. LR has served as a speaker, or has received education funding from MSD, AbbVie, Adacyte, Takeda, Pfizer, Janssen and Ferring. FC has served as a speaker, or has received research or education funding or advisory fees from Takeda, Janssen, MSD and Ferring. ED has served as a speaker and has received research and educational funding and advisory fees from AbbVie, Adacyte Therapeutics, Biogen, Celltrion, Gilead, Janssen, Kern Pharma, MSD, Pfizer, Roche, Samsung, Takeda, Tillotts and Thermofisher. The remaining authors declare no conflicts of interest.

Author Contributions

MC and ED designed the study, performed statistical analyses, interpreted the results and drafted the manuscript. FC and MM participated in the statistical analysis, and critically reviewed the manuscript. The remaining authors included patients and critically reviewed the manuscript. All authors are aware and agree to the content of the manuscript and accept their authorship.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Appendix

Complete list of the affiliations of the ENEIDA-GETECCU investigators:

Margalida Calafat: H.U. Germans Trias i Pujol [Badalona] and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [Madrid]; Míriam Mañosa: H.U. Germans Trias i Pujol [Badalona] and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [Madrid]; Elena Ricart: H. Clínic Barcelona [Barcelona], IDIBAPS [Barcelona] and Centro de Investigació Biomédica en Red de Enfermedades Hepáticas y Digestivas [Madrid]; Pilar Nos: H. Universitari La Fe [València] and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [Madrid]; Eva Iglesias: H. Reina Sofía [Córdoba]; Isabel Vera: H.U. Puerta de Hierro Majadahonda [Madrid]; Antonio López-Sanromán: H.U. Ramón y Cajal [Madrid]; Jordi Guardiola: H.U. Bellvitge [L'Hospitalet de Llobregat]; Carlos Taxonera: H.U. Clínico San Carlos [Madrid] and Instituto de Investigación del Hospital Clínico San Carlos [Madrid]; Miguel Mínguez: H.U. Clínico de València [València] and Universitat de València [València]; M. Dolores Martín-Arranz: H.U. La Paz [Madrid]; Luisa de Castro: Complexo H.U, de Vigo [Vigo]; Ruth de Francisco: H.U. Central de Asturias and Instituto de Investigación Biosanitaria del principado de Asturias [ISPA], [Oviedo]; Montserrat Rivero: H.U. Marqués de Valdecilla [Santander] and IDIVAL [Santander]; Esther Garcia-Planella: H.U. de la Santa Creu i Sant Pau [Barcelona]; Xavier Calvet: H.U. Parc Taulí [Sabadell] and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [Madrid]; Santiago García-López: H.U. Miguel Servet [Zaragoza]; Lucía Márquez: Servei de Digestiu, Hospital del Mar [Barcelona] and IMIM [Hospital del Mar Medical Research Institute] [Barcelona]; Fernando Gomollón: H. Clínico Lozano Blesa [Zaragoza], Instituto de Investigaciones Sanitarias de Aragón and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [Madrid]; Jesús Barrio: Servicio de Gastroenterología. Hospital Universitario Río Hortega. Gerencia Regional de Salud de Castilla y León [SACYL] [Valladolid]; Maria Esteve: H. Universitari Mútua Terrassa [Terrassa] and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [Madrid]; Fernando Muñoz: Hospital Universitario de Salamanca [Salamanca]; Javier P. Gisbert: H. U. de la Princesa [Madrid], Instituto de Investigación Sanitaria Princesa [IIS-IP], Universidad Autónoma de Madrid [UAM] and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [Madrid]; Ana Gutiérrez: H. G. U. Alicante, [Alicante], Instituto de Investigación Sanitaria y Biomédica de Alicante [ISABIAL] and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [Madrid]; Joaquín Hinojosa: Hospital Vithas 9 de Octubre [València]; Federico Argüelles-Arias: Servicio de Aparato Digestivo, Hospital Universitario Virgen Macarena [Sevilla] and Profesor Facultad Medicina de la Universidad de Sevilla [Sevilla]; David Busquets: H.U.Girona Dr. J. Trueta [Girona]; Luís Bujanda: Instituto Biodonostia, Universidad del País Vasco [UPV/EHU] [San Sebastián] and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [Madrid]; José L Pérez-Calle: H.U. Fundación de Alcorcón [Alcorcón]; Beatriz Sicilia: Hospital Universitario de Burgos [Burgos]; Olga Merino: H. de Cruces [Barakaldo]; Pilar Martínez: H. 12 de Octubre [Madrid]; Fernando Bermejo: Hospital Universitario de Fuenlabrada and Instituto de Investigación Sanitaria del Hospital La Paz [IdiPAZ], [Madrid]; Rufo Lorente: H. General de Ciudad Real [Ciudad Real]; Manuel Barreiro-de Acosta: C.H.U. Clínico Santiago [Santiago de Compostela]; Cristina Rodríguez: C.H. de Navarra [Pamplona]; Mariana Fe García-Sepulcre: H.G. Elche [Elche]; David Monfort: Consorci Sanitari de Terrassa [Terrassa]; Patricia Romero: H. Santa Lucía Cartagena [Cartagena]; Carlos Tardillo: H. U. Ntra Sra. de Candelaria [Santa Cruz de Tenerife]; Óscar Roncero: H. Mancha Centro [Alcázar de San Juan]; Jordina Llaó: H. Sant Joan de Déu-Althaia [Manresa]; Guillermo Alcaín: H. Clínico de Málaga [Málaga]; Núria Rull: H. Universitari Son Llàtzer [Palma]; Mónica Sierra-Ausín: C. Asistencial Universitario de León [CAULE] [León]; Luís Fernández-Salazar: Servicio de Aparato Digestivo. Hospital Clínico Universitario de Valladolid, SACYL and Universidad de Valladolid [Valladolid]; Jair Morales-Alvarado: H.G. de Granollers [Granollers]; Mercè Navarro-Llavat: H. Moisès Broggi [St.Joan Despí]; Miguel A. Montoro: H. Universitario San Jorge [Huesca]; Carmen Muñoz-Villafranca: H. Universitario de Basurto [Bilbao]; Alfredo J. Lucendo: Department of Gastroenterology. Hospital General de Tomelloso [Ciudad Real], Instituto de Investigación Sanitaria Princesa [IIS-IP] [Madrid] and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas

[Madrid]; Manuel Van Domselaar: H. Torrejón [Madrid]; Ainhoa Rodríguez-Pescador: H. de Galdakao [Vizcaya]; José M.Huguet: H.G.U. de València [València]; Laura Ramos: H. Universitario de Canarias [La Laguna]; Sandra Estrecha: H.U. Araba [Vitoria]; Pedro Almela: H. General de Castelló [Castelló]; Ramón Pajares: H. Infanta Sofía [San Sebastián de los Reyes]; Sam Khorrami: H. Son Espases [Palma]; Rosa Eva Madrigal: C.H. de Palencia [Palencia]; Eva Sesé: H.U. Arnau de Vilanova [Lleida]; Ana Mª Trapero: C.H. de Jaén [Jaén]; Jesús Legido: H. General de Segovia [Segovia]; Pau Gilabert: H. de Viladecans [Viladecans]; Fiorella Cañete: H.U. Germans Trias i Pujol [Badalona] and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [Madrid]; Eugeni Domènech: H.U. Germans Trias i Pujol [Badalona] and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas [Madrid].

References

1. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009;361:2066–78.
2. Everhov ÅH, Halfvarson J, Myrelid P, *et al*. Incidence and treatment of patients diagnosed with inflammatory bowel diseases at 60 years or older in Sweden. *Gastroenterology* 2018;154:518–28.e15.
3. Mañosa M, Calafat M, de Francisco R, *et al*.; GETECCU. Phenotype and natural history of elderly onset inflammatory bowel disease: a multicentre, case-control study. *Aliment Pharmacol Ther* 2018;47:605–14.
4. Parian A, Ha CY. Older age and steroid use are associated with increasing polypharmacy and potential medication interactions among patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2015;21:1392–400.
5. Ha CY, Katz S. Clinical outcomes and management of inflammatory bowel disease in the older patient. *Curr Gastroenterol Rep* 2013;15:310.
6. Cross RK, Wilson KT, Binion DG. Polypharmacy and Crohn's disease. *Aliment Pharmacol Ther* 2005;21:1211–6.
7. Klotz U. Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev* 2009;41:67–76.
8. Fulop T, Witkowski JM, Olivieri F, Larbi A. The integration of inflammaging in age-related diseases. *Semin Immunol* 2018;40:17–35.
9. Pera A, Campos C, López N, *et al*. Immunosenescence: implications for response to infection and vaccination in older people. *Maturitas* 2015;82:50–5.
10. Pawelec G. Age and immunity: what is "immunosenescence"? *Exp Gerontol* 2018;105:4–9.
11. Hanauer SB, Feagan BG, Lichtenstein GR, *et al*.; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359:1541–9.
12. Fidder H, Schnitzler F, Ferrante M, *et al*. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009;58:501–8.
13. O'Meara S, Nanda KS, Moss AC. Antibodies to infliximab and risk of infusion reactions in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2014;20:1–6.
14. Feuerstein JD, Cullen G, Cheifetz AS. Immune-mediated reactions to anti-tumor necrosis factors in inflammatory bowel disease. *Inflamm Bowel Dis* 2015;21:1176–86.
15. Ben-Horin S, Chowers Y. Review article: Loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther* 2011;33:987–95.
16. Ben-Horin S. Loss of response to anti-tumor necrosis factors: what is the next step? *Dig Dis* 2014;32:384–8.
17. Farrell RJ, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. *Gastroenterology* 2003;124:917–24.
18. Baert F, Noman M, Vermeire S, *et al*. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;348:601–8.
19. Beaugerie L, Brousse N, Bouvier AM, *et al*.; CESAME Study Group. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;374:1617–25.
20. Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology* 2018;155:337–46.e10.
21. Calafat M, Mañosa M, Cañete F, *et al*.; ENEIDA registry of GETECCU. Increased risk of thiopurine-related adverse events in elderly patients with IBD. *Aliment Pharmacol Ther* 2019;50:780–8. Erratum in: *Aliment Pharmacol Ther* 2020;51:674.
22. Zabana Y, Panés J, Nos P, *et al*.; en representación de GETECCU. The ENEIDA registry (Nationwide study on genetic and environmental determinants of inflammatory bowel disease) by GETECCU: design, monitoring and functions. *Gastroenterol Hepatol* 2020;43:551–8.
23. Viola A, Monterubbianesi R, Scalisi G, *et al*.; Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). Late-onset Crohn's disease: a comparison of disease behaviour and therapy with younger adult patients: the Italian Group for the Study of Inflammatory Bowel Disease 'AGED' study. *Eur J Gastroenterol Hepatol* 2019;31:1361–9.
24. Cottone M, Kohn A, Daperno M, *et al*. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011;9:30–5.
25. Choquette D, Faraawi R, Chow A, Rodrigues J, Bensen WJ, Nantel F. Incidence and management of infusion reactions to infliximab in a prospective real-world community registry. *J Rheumatol* 2015;42:1105–11.
26. Crandall WV, Mackner LM. Infusion reactions to infliximab in children and adolescents: frequency, outcome and a predictive model. *Aliment Pharmacol Ther* 2003;17:75–84.
27. Cannon JG, St Pierre BA. Gender differences in host defense mechanisms. *J Psychiatr Res* 1997;31:99–113.
28. Levartovsky A, Ungar B, Yavzori M, *et al*. Infliximab levels and antibodies in IBD-related peripheral arthralgia. *Int J Colorectal Dis* 2020;35:1141–8.
29. Shivaji UN, Sharratt CL, Thomas T, *et al*. Review article: Managing the adverse events caused by anti-TNF therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2019;49:664–80.
30. Porcari S, Viola A, Orlando A, *et al*.; Sicilian Network for Inflammatory Bowel Diseases (SN-IBD). Persistence on anti-tumour necrosis factor therapy in older patients with inflammatory bowel disease compared with younger patients: data from the Sicilian Network for Inflammatory Bowel Diseases (SN-IBD). *Drugs Aging* 2020;37:383–92.
31. Lobatón T, Ferrante M, Rutgeerts P, Ballet V, Van Assche G, Vermeire S. Efficacy and safety of anti-TNF therapy in elderly patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2015;42:441–51.
32. Paul S, Roblin X. Letter: Immunogenicity of anti-TNF in elderly IBD patients. *Aliment Pharmacol Ther* 2019;50:336.
33. Desai A, Zator ZA, de Silva P, *et al*. Older age is associated with higher rate of discontinuation of anti-TNF therapy in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:309–15.
34. de Jong ME, Smits LJT, van Ruijven B, *et al*. Increased discontinuation rates of anti-TNF therapy in elderly inflammatory bowel disease patients. *J Crohns Colitis* 2020;14:888–95.