

Original article

Systematic review: Safety and efficacy of anti-TNF in elderly patients

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ABSTRACT

Objective: To evaluate whether the safety and efficacy of anti-TNF treatments in elderly patients with rheumatic diseases is similar than the safety and efficacy of the same drugs in younger patients.

Methods: Systematic review. We performed a systematic search in MEDLINE (Pubmed), EMBASE (Ovid), and the Cochrane Library Plus. Abstracts published in the American and European rheumatology congresses and articles in Reumatología Clínica were also reviewed.

Results: Ten studies fulfilled the inclusion criteria. Studies show a similar efficacy in elderly and younger patients. The differences between the young and the elderly regarding DAS28 reductions before and after are very small: 0.04 in the Geneway et al study and 0.0 in the Mariette et al study, as well as in the before and after HAQ: 0.04 (Geneway et al), 0.18 (Schiff et al) and 0.06 (Mariette et al). Adverse events reported in elderly and younger patients are 83.3% and 77.1% respectively with etanercept, as reported by Fleischmann; 27.2% vs 12.5%, $P=0.19$, as reported by Chevillotte, and the rate of withdrawal due to an adverse event was 57.8% vs 29.2% with infliximab, $P=0.03$, 36% vs 15% $P=0.06$ with adalimumab and 10.3% and 9.5%, with no significant P value, as reported by Massara.

Conclusions: The information to assess the efficacy and safety of anti-TNF therapy in elderly patients was obtained in all cases from sub analyses and therefore bias is possible. We can say, with a low to moderate level of evidence, that elderly patients undergoing anti-TNF treatments have a higher number of adverse events, and similar efficacy, when compared with younger patients.

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Revisión sistemática: eficacia y seguridad del tratamiento anti-TNF en pacientes ancianos

RESUMEN

Palabras clave:

Anti TNF

Ancianos

Seguridad

Eficacia

Terapia biológica

Objetivo: Evaluar si la seguridad y la eficacia de los tratamientos anti TNF en pacientes ancianos con enfermedades reumáticas inflamatorias son similares a la seguridad y eficacia en pacientes jóvenes.

Métodos: Revisión sistemática. Se realizó una búsqueda bibliográfica en Medline (vía Pubmed), Embase (vía Ovid) y Cochrane Library Plus, abstracts publicados en los congresos americano y europeo de reumatología y artículos publicados en Reumatología Clínica.

Resultados: Diez estudios cumplían los criterios de inclusión. Los estudios coinciden en una eficacia similar en jóvenes y ancianos. Las diferencias en la reducción del DAS28 de antes y después entre jóvenes y ancianos son muy pequeñas: 0,04 en el estudio de Geneway et al y 0,0 en el de Mariette et al; así como en el HAQ de antes y después: 0,04 (Geneway et al), 0,18 (Schiff et al) y 0,06 (Mariette et al).

Los efectos adversos descritos en ancianos y jóvenes respectivamente son de 83,3% y 77,1% con etanercept, según Fleischmann; 27,2% vs. 12,5%, $p = 0,19$, según Chevillotte; y 57,8% vs. 29,2% con infliximab, $p = 0,03$, 36% vs. 15%, $p = 0,01$ con adalimumab y de 10,3% vs. 9,5% con etanercept, p no significativa, según Massara.

Conclusiones: La información para evaluar la eficacia y seguridad de los anti TNF en ancianos procede de sub-análisis y por tanto se encuentra sujeta a sesgos. Podemos decir, con un nivel de evidencia bajo o moderado, que los ancianos presentan más acontecimientos adversos y similar eficacia que en los no ancianos cuando se tratan con agentes anti TNF.

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Introduction

The prognosis of patients with inflammatory joint diseases has greatly improved in the last few years, thanks mainly to the introduction of biological therapies. We are more and more conscious that many patients affected by an inflammatory arthropathy will present radiological, functional and social deterioration during their illness. That is why disease-modifying anti-rheumatic drug (DMARD) treatment is set up as soon as possible to reduce damage. Approximately a third of patients do not respond to conventional DMARD treatment, so they consequently receive some type of biological therapy. These treatments present side effects that we should be aware of.

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects 0.5%-1% of the population.¹ Although the greatest incidence of rheumatoid arthritis is seen in the group between 30-50 years old, approximately 20%-30% of RA patients are diagnosed after they are 60 years old; given that it is a chronic illness, epidemiological studies show that RA prevalence is greater in a population over 65 years old, with the mean age for our sample RA populations being 60-65 years old.² Something similar occurs in the case of psoriatic arthritis (PA) and ankylosing spondylitis (AS). These two diseases normally appear before the age of 40 and are unusual after 65 years old, but being chronic illnesses, which rarely remit for long, they continue during the whole of the person's life.

Despite the fact that elderly patients are the largest group, they are frequently excluded from clinical trials. That explains why little information on the efficacy and safety of these treatments in elderly people is available.

The likelihood of there being adverse effects in an elderly population is increased, due to changes in their metabolism. Elderly patients also present more comorbidities, which require concomitant treatment, entailing a greater probability of drug interaction.

As quite a significant number of RA patients having rheumatology surgeries are in the age range of over 65 years old, it is important to be able to reply to the question of whether the benefit risk ratio of anti-TNF therapies is maintained in this group.

Methods

A systematic review was undertaken to assess whether the efficacy and safety of anti-TNF treatments are similar in elderly patients to those of young patients. A reviewer (NB) designed the search strategy carried out the study selection and collected all the data, under the supervision of somebody else with experience (LC).

The criteria used for study selection in this review were as follows: 1) by patient type, which would include the elderly (over 65 years old) in the study groups for RA, AS, and PA; 2) by study type, in which there were no limitations, except narrative reviews and case series of fewer than 10 patients; and 3) by measured results, which would include efficacy and safety measures.

Search strategy

A bibliographical search was carried out (available in the annex) on Medline via Pubmed (1976–September 2008) and Embase via Ovid (1980–September 2008). The search included terms that identified the different anti-TNFs and also included terms that defined the elderly. The search was limited to humans and articles in Spanish, English, and French. The terms infliximab, etanercept, adalimumab and elderly were also introduced as searches in the Cochrane Library. Abstracts presented at American College of Rheumatology (ACR) (2002-2007) and European League against Rheumatism (EULAR) (2002-2008) congresses were reviewed, as well as articles published on anti-TNF in *Reumatología Clínica*

(2005-2008). Only abstracts that were available on-line at the time of the review were included.

Study selection

Taking these inclusion criteria into account, an initial selection was made of the studies recovered by the search strategies starting from titles and continuing with a summary selection. All the articles whose summary showed that the article could contain information needed for the review, as well as those with a doubtful title and without a summary, were obtained for the detailed study. Once the articles had been recovered, the reference lists were reviewed to check if possibly related articles existed that were not recovered by the search strategy.

Quality assessment and evidence level

The initial intention was to include any format, not only clinical trials. However, given that there were no horizontal scales that allow all designs to be assessed, we decided to set up quality control according to the specific parameters of design type. The evidence level for each study was consequently set up based on the Evidence levels for the Oxford Centre for Evidence-Based Medicine.³ According to this scale, the levels for questions on efficacy and security would be as follows:

- 1a) systematic review of clinical trials with homogeneity
- 1b) individual clinical trial with a narrow confidence interval
- 1c) clinical trial with an "all or none" result
- 2a) systematic review of cohort studies with homogeneity
- 2b) individual study of cohorts or poor quality clinical trial (e.g., <80% follow-up)
- 2c) investigation on health results, ecological studies
- 3a) systematic review of case control studies with homogeneity
- 3b) individual case control study
- 4) series of cohort cases and studies or poor quality control cases
- 5) expert opinion without explicit critical appraisal or based on physiology, basic science or principles

Evidence synthesis

Data collection sheets were created, adapting them to the investigation question. The following information on the selected studies was gathered: number of elderly subjects in the study, illness that they suffered from, biological treatment received and its dosage, length of study, variables with which the authors assessed the safety and efficacy of the biological treatment, quality of the study and conclusions the study came to. With this data, an evidence table on which to base the qualitative analysis was set up.

Results

Search results are detailed in Figure. A total of 10 studies were included, which came to a total of 4,997 patients over 65 years old treated with anti-TNF agents, although it may be possible that some patients are included in more than one study. The majority of data comes from retrospective clinical trial sub-analyses, although also from analyses of registers of patients receiving biological treatment and from administrative data bases with health information. In Table 1 there is a description in publishing order of the studies included,⁴⁻¹³ showing the variables used to assess the efficacy and safety in each study. Quality is moderate, with an evidence level that varies between 2a (3 studies) and 4 (3 studies). It can be said that all the evidence comes from RA studies, given that the number of patients with other diseases is small (265 PA and 276 AS). The excluded studies are described in Table 2.¹⁴⁻²⁰

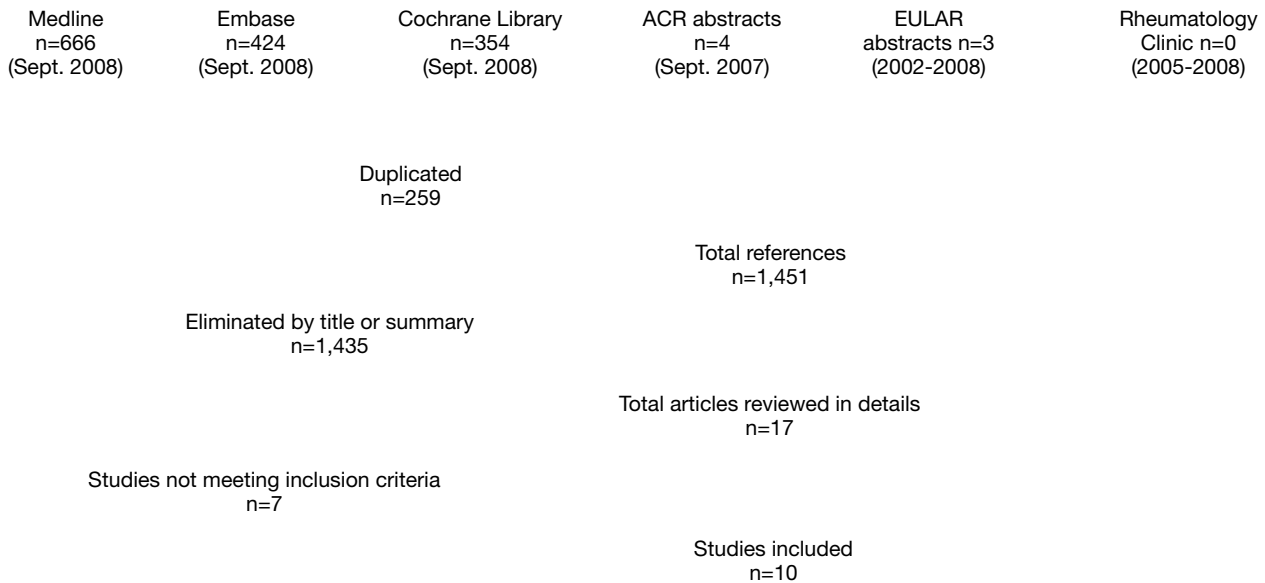


Figure 1. Selection study flowchart.

The majority of these patients were treated with etanercept.^{7-9,13} There were some articles which included patients treated with infliximab,^{11,12} and an abstract was found where the ACR assessed safety and efficacy in patients with adalimumab.¹⁰ In other articles the type of anti-TNF used was not specified.^{4,5} Anti-TNF treatment was administered as monotherapy or combined with methotrexate.

The majority of articles considered an elderly patient as one older than 65 years, except one article that analysed patients over 70 years old.¹²

Safety of etanercept treatment

The safety of etanercept treatment in the elderly is assessed in the Fleischmann et al study (2006).⁸ Patients with rheumatic diseases that had taken part in efficacy and safety studies with etanercept are assessed: patients with RA (18 trials), psoriatic arthritis (2 trials) and ankylosing spondylitis (2 trials). Safety data for patients administered at least one dosage of etanercept were collected.

In this study, the proportion of patients that presented adverse effects (AE) and important adverse effects (IAE) was apparently greater in patients over 65 years old, whether they were treated with etanercept or not: 126/170 (74.1%) AE in patients over 65 years old in the control group; 400/480 (83.3%) AE in patients over 65 years old in the group treated with etanercept; 647/1,020 (63.4%) AE in young patients in the placebo group; and 2,046/2,652 (77.1%) AE in young patients treated with etanercept. However, when the proportional difference was compared between AE and IAE (the difference between the AE/IAE percentage in patients treated with etanercept and treated with a placebo), there were no significant differences between patients over 65 years old and those younger. Patients under 65 years old presented more infections than those over 65 years old as there was a greater number of upper respiratory tract infections: 1,470/2,652 (55.4%) young patients with infections in the group treated with etanercept, 406/1,020 (39.8%) infections in the control group for the young, 234/480 (48.8%) infections in elderly patients in the group treated with etanercept, and 87/170 (51.2%) infections in the control group of the elderly. However, it should be emphasised that patients over 65 years old presented

a greater number of infections that required hospitalisation, but this difference was not statistically significant when comparing it to subjects under 65 years old (10.4% in the elderly treated with etanercept, 7.1% in the elderly control group, 4% in the young treated with etanercept, and 1.3% in the control group for the young). No cases of tuberculosis were reported in any of the groups. There were no differences in recorded cardiovascular events (CE) (57/650 [8.8%] in elderly patients: Fifty treated with etanercept and 7 with a placebo presented CE; 83/3672 [2.3%] patients: Seventy-eight treated with etanercept and 5 with a placebo presented CE). There are 8 reported cases of demyelinating disease in patients under 65. There were no cases of demyelinating disease in the elderly. The number of cases with reported neoplasms (including lymphomas) remained stable during the period and was similar in the elderly and young, and similar or less than that expected in a RA population. The number of deaths was similar in the young to that in the elderly, when the rates were adjusted for age and gender, but differed in causes. The main cause of death in those over 65 years old was cardiovascular, and it was due to gastrointestinal causes or neoplasms in those under 65 years old.

In the Fleischmann et al study of 2003,⁹ treatment with etanercept was well tolerated. The majority of adverse effects were slight and occurred in a similar frequency in both groups, except for local reactions to injections (in cases/patient-year) (4.31 vs 1.47, $P=.036$), headache (0.37 vs 0.18, $P<.001$) and rhinitis (0.19 vs 0.10 $P=.006$), which were more frequent in the young, and infections (1.56 vs 1.36, $P=.036$), which were more frequent in the elderly.

Medically important infections (that required hospitalisation or intravenous antibiotic treatment) were not very frequent [31/931 (3%) of patients under 65 years old, and 14/197 (7%) in patients >65 years old]. These infections were more frequent in patients over 65 years old in a significantly statistical way. The adjusted values for exposure time were 0.09 against 0.04 events/patients/year ($P=.003$). In the group of patients over 65 years old, 5 deaths were reported. Their causes were accidental injury, cardiac failure, lung cancer, ovarian cancer and infection. The expected death rate for a population of this size in individuals >65 years old is 6.5. In the population <65 years old, 3 deaths were reported due to lung cancer, heart attack

Table 1

Evidence table for studies included in the review

Author, origin (date of publication)	Design, follow-up and evidence level	Patients	Intervention	Variables used for assessment	
				Efficacy	Safety
Genevay et al, Switzerland (2007)	Biological register	RA	Anti-TNF	DAS 28	Discontinuation of treatment due to AE
	2 years Evidence level 2b	n=1,571 ≥65 yrs=344 <65 yrs=1,227		HAQ EULAR response RADAI	
Schneeweiss et al, USA (2007)	Administrative DB review from the Pennsylvania Health System	RA	Methotrexate	NA	Serious bacterial infections
	8 years Evidence level 4	n=15,597 (469 treated with anti-TNF) ≥65 yrs=all	Other DMARD Anti-TNF GC		
Massara et al,* Italy (2007)	Retrospective DB analysis from a third party hospital	RA	Infliximab	NA	Adverse effects
	Evidence level 4	n=309 ≥65 yrs=73 <65 yrs=236	Etanercept Adalimumab		
Schiff et al, USA (2006)	Meta-analysis of 3 CE and 2 extensions	RA	Etanercept	• HAQ-DI • VAS • DAS 28	NA
	Evidence level 2a	ERA: ≥65 yrs=37; <65 yrs=170 LRA: ≥65 yrs=20 TEMPO: ≥65 yrs=50; <65 yrs=173 ERA extension: ≥65 yrs=69; <65 yrs=47 LRA extension: ≥65 yrs=69; <65 yrs=49			
Fleischmann, USA (2006)	Meta-analysis of 22 ECs	RA	Etanercept	NA	<ul style="list-style-type: none"> • Adverse effects • Infections • Medically important infections • Cardiovascular diseases • Neoplasms • Deaths
	Evidence level 2a	PA ≥65 yrs=14 <65 yrs=251 AS ≥65 yrs=4 <65 yrs=272			
Bathon et al, USA (2006)	Meta-analysis of 3 CT and 2 extensions	RA	Etanercept	• HAQ • Radiological damage • ACR criteria	<ul style="list-style-type: none"> • Adverse effects • Serious infections • Opportunistic infections • Neoplasms
	Evidence level 2a	≥69 yrs=37; <65 yrs=355 ERA: ≥ LRA: ≥65 yrs=39; <65 yrs=208 TEMPO: ≥65 yrs=141; <65 yrs=541 ERA extension: ≥65 yrs=64; <65 yrs=404 LRA extension: ≥65 yrs=93; <65 yrs=488			
Mariette et al,* France, Spain, Germany (2006)	Multicentre EC (REACT Trial)	RA	Adalimumab	• DAS 28 • HAQ	• Adverse effects
	Evidence level 2b	<40 yrs=1,002 40-65 yrs=4,125 66-75 yrs=1,245 > 75 yrs=238			
Dabbous et al,* Japan (2006)	Observation study	RA	Infliximab	3 items scale	<ul style="list-style-type: none"> • TBC • Infusion reactions
	Evidence level 4	<45 yrs=905 45-54 yrs=1,213 55-64 yrs=1,692 65-74 yrs=1,003 >75 yrs=187			
Chevillotte et al, France (2005)	Observation study of DB in 9 hospitals in 1 year	RA=60 AS=23	Infliximab	Discontinuation due to inefficacy	<ul style="list-style-type: none"> • Adverse reactions • Serious infections
	Evidence level 4	≥70 yrs=11			
Fleischmann et al, USA (2003)	Meta-analysis of 4 CE and 5 extensions	RA	Etanercept	• ACR 20 • ACR 50 • ACR 70 • NPJ, NSJ	• Adverse effects
	Evidence level 2a	No.=1,128 <65 yrs=931 >65 yrs=197			

AE indicates adverse event; AS, ankylosing spondylitis; CT, clinical trial; DB, database; DLQI, dermatology life quality index; ERA, early RA randomized etanercept study GC: glucocorticoids; HAQ-DI: health assessment questionnaire disease index; LRA, late RA randomized etanercept study; NA, not assessed; NPJ, number of painful joints; NSJ, number of swollen joints; PA, psoriatic arthritis; RA, rheumatoid arthritis; TBC, tuberculosis; TEMPO, trial of etanercept and methotrexate with radiographic patient outcomes; yrs, years.

* Data obtained from a congress abstract.

Table 2
Excluded studies and reasons for exclusion

Study (year) (reference)	Exclusion reasons	Type of study	Reference of the study in which it is included
Fleischmann (2007) ¹⁴	Duplicated data	Review	8,9
Salliot et al (2007) ²¹	Does not fit the investigation question (it assesses the infection rate in patients with rheumatic diseases before and after anti-TNF treatment)	Cohort study	Not included in the results
Díaz-Borjon et al (2006) ¹⁵	Does not fit the investigation question (it describes the different options for biological treatments in RA, spondyloarthropathies, and other rheumatic diseases, its action mechanism and efficacy, but not specifically in the elderly)	Review	Not included in the results
Fleischmann (2006) ¹⁶	Duplicated data	Review	8,9
Ornetti et al (2006) ¹⁷	Duplicated data	Review	4,8,9,12,13,18,19,21,22
Harrison (2005) ¹⁸	Safety and efficacy are not assessed. Compares the treatment rate used in the young and elderly	Case control study	Not included in the results
Legrand JL et al (2005) ¹⁹	It assesses the treatments used in elderly patients with arthritis, including anti-TNFs, treatment survival, and infection rate during treatment, but it does not compare the control group	Cohort study	Not included in the results
Maillard et al (2005) ²²	Does not fit the investigation question (It assesses the pyogenic infection rate in patients with anti-TNF treatment; it does not compare the rate in the elderly to that of the young)	Cohort study	Not included in the results
Zih et al (2003) ²⁰	Does not fit the investigation question (it describes the anti-TNF treatments for inflammatory arthritis and vasculitis, but not specifically in the elderly)	Review	Not included in the results

and aortic aneurysm. Cancer was diagnosed in 9 patients under 65 years old (breast cancer (2 cases), lung (2 cases), ovarian (2 cases), bile duct adenocarcinoma (1 case), Hodgkin's disease (1 case) and non-Hodgkin lymphoma of the parotid). Death occurred in 5 patients over 65 years old [prostate cancer (2 cases), lung cancer (2 cases), and Hodgkin's disease (1 case)]. The number of neoplasm cases expected by the authors was 8.4 for those under 65 years of age and 5.5 for those over.

The Bathon et al⁹ study also assesses the safety of treatment with etanercept, using information from patients that took part in controlled LRA and ERA clinical trials, LRA and ERA extension studies, and the TEMPO study. In the LRA and ERA study control groups, the rates for adverse effects per patient/year tended to be higher in elderly patients than in younger ones (LRA: 0.510 vs 0.108; ERA: 0.417 vs 0.072). When comparing treatment groups in the controlled LRA study, the adverse effect rate was greater in the group of elderly treated with a placebo (0.510), in comparison to those treated with etanercept (0.116). However, the rates were comparable in both treatment groups of younger patients (0.108 vs 0.090). In the controlled ERA study, the adverse effect rate was greater in the group treated with methotrexate for both age groups (0.417 vs 0.32 in the elderly and 0.072 vs 0.046 in the young). In the TEMPO study, the adverse effects were similar in the elderly and young treated with methotrexate (0.240 vs 0.227). In contrast, the AS rates were much higher in the elderly compared to the young in the etanercept group (0.360 vs 0.147) and in the etanercept+methotrexate group (0.242 vs 0.095).

Infection rates were similar in the elderly in controlled ERA and LRA studies, except for the elderly treated with etanercept in the LRA study, where no infections were reported (0.680 vs 0.036 in the placebo group and 0 vs 0.140 in the etanercept group of the LRA study and, in the ERA study, 0.074 vs 0.016 in the MTX group and 0.095 vs 0.010 in the etanercept group). Other comparisons between treatment groups report similar rates for infections in controlled ERA and LRA studies. In the TEMPO study, the infection rates were similar between the treatment groups and between age groups. Infection rates in ERA and LRA extension studies showed similar infection rates in their respective controlled studies. The 5 most frequent infections in the LRA and ERA extension studies were pneumonia, cellulite, unspecified infection, bacterial arthritis and bronchitis. The neoplasm rates were low.

The authors say that in the extension studies of these studies there was a higher cancer rate in elderly patients than in younger ones, but the number of cancer cases was no different from that expected in the general population. The number of lymphomas was greater than that expected in the general population, except in the ERA group for the elderly, where no lymphomas were detected. There were no opportunistic infections in the elderly indicated in any of the studies. There were 4 opportunistic cases in the young: Candida cystitis (2 cases), gastrointestinal candidiasis (1) and chicken pox (1). No cases of tuberculosis were reported.

Efficacy of etanercept treatment

Treatment efficacy with etanercept in elderly patients is assessed in an article by Schiff et al,⁷ which includes patients that come from ERA, LRA and TEMPO studies, through HAQ and VAS.

Baseline HAQ-DI was similar in ERA and TEMPO studies and worse in the elderly in the LRA study ($P < .05$). Both elderly and young groups showed an improvement in HAQ-DI with respect to the baseline during the first 3 months (0.39-0.92 in the young, and 0.57-1.00 in the elderly). Improvements were maintained in ERA and LRA extension studies for both age groups during the 48 months of treatment. In ERA, LRA and TEMPO studies, 60%-88% of patients achieved an improvement in HAQ-DI of at least 0.22, with a similar response in both age groups. The patient proportion that showed worsening in HAQ results was 2%-16% in the elderly and 2%-6% in the young. The patient proportion that showed an HAQ of 0 was 4%-27% in the elderly and 10%-33% in the young.

Basally, patients over 65 years old showed worse HAQ values than younger patients. This was attributed to the fact that disability is associated with pathologies such as osteoarthritis that are more common in the elderly. Improvement in HAQ was similar in young and elderly patients.

Baseline VAS was similar in the young and elderly (5.82-6.78 in the young, and 6.07-6.85 in the elderly), reaching a plateau 3-6 months after treatment was started. At the end of treatment, VAS was 2.54-3.88 in the elderly and 2.44-3.38 in the young.

In the Bathon et al⁹ study concerning HAQ, baseline HAQs were worse in elderly patients. In the LRA study, the mean HAQ improvement from the baseline in the elderly treated with etanercept was 0.46 (SD 0.52) at 6 months. Improvements in HAQ were similar in both age

groups. In ERA, the improvement was parallel in the young and at 24 months was 0.46 (SD 0.66) for the elderly treated with etanercept. In TEMPO, the improvement with respect to the baseline in patients treated with etanercept at 12 months was 0.71 (SD 0.78) and 0.92 (SD 0.70) in those treated with etanercept and methotrexate.

There were similar improvement levels in the elderly and young, despite the fact that the elderly showed a higher level of improvement with the etanercept and methotrexate combination than with monotherapy, when compared to the young.

With regards to ACR response, in the LRA study, the elderly treated with etanercept had similar ACR responses, or slightly lower, compared to the young at 6 months (ACR 20/50/70 of 70%/45%/15% in the elderly vs 65%/39%/15% in the young). In the ERA study, the response tended to be lower in the elderly than in the young at 24 months (ACR 20/50/70 of 54%/22%/14% in the elderly vs 77%/54%/32% in the young). In the TEMPO study, the elderly showed a greater increase in efficacy than the young during combined treatment with etanercept and methotrexate, rather than with monotherapy.

With regards to radiological progression, the baseline TSS (total Sharp Score) in all treatment groups was greater in the elderly compared to the young. Despite baseline differences, the response patterns were similar in the young [-0.73 (SD 0.24)] and in the elderly [TSS of 0.27 (SD 0.70)].

The interesting point of the Fleischmann study¹³ is that it assesses response during at least a year. The responses were quick and held in the two comparison age groups. A similar percentage of both age groups achieved an ACR 20/50/70 (69%/44%/20% vs 66%/40%/15% in the young and elderly respectively, $P=.480$). The proportion of patients with early RA achieving an ACR of 20 was similar in both age groups (58% vs 51% in the young and elderly respectively, $P=.265$). The findings were comparable in patients with long-term RA, for both age groups. Etanercept treatment also showed a quick improvement in the number of tender joints and those with tumours, in both cases.

Safety of infliximab treatment

There is an observational study by Chevillotte et al,¹² where 83 patients with RA and AS that come from a database of 9 hospitals in Borgoña are assessed; of these patients, 11 were over 70 years old, which is where a greater percentage of serious infections is seen. Discontinuation of therapy because of serious infections was greater in the elderly, but not significantly, being 18.2% in the elderly and 2.8% in the young ($P=.08$). No differences were found with regards to adverse effects (27.2% in the elderly and 12.5% in the young, $P=.19$) and allergic reactions (9.1% in the elderly and 6.9% in the young, $P=.59$) in both age groups.

There is also a study published in abstract form in the ACR¹¹ that assesses 5,000 patients with rheumatoid arthritis from a post-marketing investigation study on infliximab in Japan. The results for safety were similar in elderly and young patients. The data they show are copied: The TBC percentage in age subgroups was 0.11% <45 years old (yr), 0.08% 45–54yr, 0.4% 55–64yr, 0.90% 65–74yr, 0.53% ≥ 75 yr, $P=.6960$; and the percentage for severe reactions to the infusion were 0.7% <45yr, 0.4% 45–54yr, 0.4% 55–64yr, 0.5% 65–74yr, 0.5% ≥ 75 yr, $P=.6960$.

Efficacy of infliximab treatment

The two studies found show similar efficacy levels in the different age groups. The Chevillotte study reports similar percentages for discontinuation of therapy because of inefficacy (0% in the elderly and 16.7% in young people, $P=.35$).

In the Dabbous study, the percentages of patients showing an improvement at 22 weeks are 91% in individuals <45yr, 91% 45–54yr, 92% 55–64yr, 92% 65–74yr and 94% ≥ 75 yr, $P=.8737$.

Efficacy and safety of adalimumab treatment

In patients treated with adalimumab, there is an abstract¹⁰ on assessing adalimumab treatment in different age groups ($n=1,002$ <40 years old, $n=4,125$ 40–65 years old, $n=1,245$ 66–75 years old and $n=238$ >75 years old), as they were patients that came from a REACT study. There were no efficacy differences assessed through DAS28 (the change in DAS28 is -2 in <75yr, and -1 ≥ 75 yr), HAQ (the mean change in HAQ is -0.4 40–65yr, -0.8 65–75yr and -0.7 ≥ 75 yr), the ACR criteria (ACR 20/50/70 are 68%/40%/18% respectively in patients of 40–65yr, 68%/35%/15% in patients of 65–75yr and 61%/35%/12% in patients of >75yr) and discontinuation due to inefficacy (7% in <65yr and 6% in >65yr), not even regarding safety amongst the different age groups (adverse effects: 8% <40yr, 10% 40–65yr, 13% 65–<75yr and 19% ≥ 75 yr; infections: 2% <40yr, 2% 40–65yr, 4% 65–75yr and 5% ≥ 75 yr).

Efficacy and safety of jointly assessed anti-TNF treatments

Genevay et al⁴ assessed the safety and efficacy of anti-TNF treatments in the elderly, including patients from a biological register in Switzerland. This included patients that had received one or more anti-TNF. The elderly patients showed improvements similar to the young patients in the DAS and RADAI efficacy levels.

Baseline DAS 28 and HAQ values were slightly higher in elderly patients.

DAS 28 showed a similar significant decrease in both treatment groups. Improvements in DAS 28 in the elderly and young respectively were -0.63 vs -0.59 one year after treatment and -0.65 vs -0.58 after 2 years.

Although HAQ decreases in both groups, at 6 months the effect is less in the elderly: in the elderly and the young (respectively) HAQ was 0.07 ± 0.02 vs 0.09 ± 0.01 , and a year later 0.08 ± 0.02 vs 0.12 ± 0.02 . The subgroup analyses showed an absence of anti-TNF effect in the patient subgroup of over 75 years of age. In these patients, HAQ worsened over the two year study due to the appearance of age-associated comorbidity.

EULAR response criteria were different in elderly and young patients. A greater percentage of the elderly were classified as having a bad response (60.2% vs 51.5%, $P<.01$) and a smaller percentage as good (7.2% vs 11.2%, $P<.05$). The authors justify this difference because EULAR response criteria depend on the absolute value of activity reached; that is why the baseline differences, although not considered clinically relevant, could have induced differences in the percentage of the respondents.

There was a similar rate in adverse effects in the young and elderly with regards to safety. We must highlight that there was a higher permanent discontinuation of therapy rate caused by allergic reactions in young people than in the elderly (10.7% in the elderly, 20% in the young). This is statistically significant when temporary discontinuation of therapy caused by allergic reactions is included ($P=.040$). There was also a higher permanent discontinuation of therapy rate for neoplasm in the elderly compared to the young (7.1% in the elderly vs 0% in young people, $P<.05$), although there are few cases of neoplasm (0 in the non-elderly and 2 in the elderly: 1 breast cancer with metastases and 1 pancreatic cancer). The neoplasms described have not been associated to anti-TNF treatment. No differences have been found for permanent discontinuation of therapy caused by infections (12% in the young vs 14.3% in the elderly, $P=.75$), nor by cardiovascular events between the 2 age groups (0% in the young vs 3.6% in the elderly, $P=.21$).

A study by Massara et al⁶ published as an abstract assesses patients with infliximab treatment ($n=19$ over 65 years old, $n=82$ under 65 years old), etanercept ($n=29$ >65 years old, $n=94$ <65 years old) and adalimumab ($n=25$ >65 years old, $n=60$ <65 years old). There is a greater percentage rate of discontinuation of therapy caused by adverse effects in patients over 65 years old that received infliximab

treatment (57.8% vs 29.2%, $P=.03$) and adalimumab (36% vs 15% $P=.06$). However, this is not the case in patients that had etanercept treatment (10.3% vs 9.5%, P =not significant).

Another study assesses the number of serious bacterial infections in elderly patients treated with anti-TNF.⁵ It assesses patients over 65 years old, with a mean age of 76.5 years. It does not compare it to the young population, but one should highlight that, in the elderly population group studied, patients with anti-TNF had an infection risk similar to patients treated with methotrexate and an infection risk smaller than those treated with glucocorticoids.

Discussion

The results of clinical efficacy and safety for anti-TNF treatment in the treatment of RA, PA, and AS have been analysed through a systematic literature review. Studies coincide with a similar efficacy in anti-TNF treatments in young and elderly patients,^{4,7,10–12} clarified by the study by Bathon,⁹ where the authors conclude that the elderly had weaker efficacy response than the young, despite the response pattern being similar in both age groups.

There are contradictory results with regards to safety. Globally, although with no statistical significance, the elderly show a higher rate of adverse effects in the studies included, except for local reactions to injections, headaches, rhinitis,¹³ allergic reactions⁴ and respiratory infections that are more frequent in the young¹³ (these latter at the expense of the upper tract infections described). Other studies report a higher infection rate in the elderly,¹² which require hospitalisation.^{8,13} On the other hand, we also find studies that report similar AS rates in young and old patients,^{5,10,11} and there is an abstract⁶ that compares different anti-TNFs, which finds more adverse effects for the elderly in patients treated with infliximab and with adalimumab, and similar results in those treated with etanercept.

With neoplasms, we find that they are reported more often for the elderly, but with a similar frequency as expected due to age.^{9,11,13} There are no unusual AS in elderly patients, nor a greater amount of adverse effects, or effects not described in the younger population.

Some reflections should be made regarding these results. Studies published to assess safety and efficacy of anti-TNF treatments in elderly patients are carried out retrospectively using databases designed for other studies, which were not specifically designed to assess the safety and efficacy of anti-TNF treatment in the elderly. This can lead to a bias, in that age groups may not be balanced in number, but also regarding other variables that are not age dependent, but that interfere with efficacy and safety results. Ideally, a subgroup analysis should have been planned in the clinical trial design phase for this reason.

Generally, clinical trials include few elderly people (which means that this population is usually under-represented) and patients with comorbidities are usually excluded. This can mean that the elderly population used for the study is not representative of the elderly population with rheumatic diseases.^{8,9} Consequently, the administrative or registry database population is more representative than the meta-analysis of clinical trials, even though the evidence level may be less. On the other hand, we are trying to undertake a data meta-analysis so as to increase global statistical power to be able to establish conclusions. However, the different study designs, and especially the different measurements for efficacy and safety examined and subgroups compared in the different studies, do not allow for this analytic approximation.

A difficult aspect to cover is the existing variability in the definition of elderly, considering anybody over 65 years old as elderly the majority of the time. In addition, the term “elderly” is not precise and does not take into consideration the differences that could exist in individuals older than 65 years old, more than 75 years old or more than 80 years old, which is why subgroup analyses are required.

In studies, the clinician decides which patients are contributors to anti-TNF treatment. This decision is normally taken carefully and it can mean a bias when data is analysed, as older patients treated could belong to an elderly patient subgroup with fewer risk factors for adverse effects than the general elderly population.^{4,12} There are also studies where there are worse activity and functional indexes at the start of treatment in the elderly population compared to the young population.^{4,7,9} This could be interpreted as more reluctance existing towards setting up anti-TNF treatment in elderly patients, which could also create a bias.

In conclusion, it seems that anti-TNF treatment has the same efficacy, or at least not less efficacy, in elderly patients than in non-elderly patients. The results are contradictory regarding safety and are based on observational studies. In our opinion, this could be interpreted to mean that in ideal conditions (such as clinical trials) safety seems reasonable, but in truer conditions (such as those in registers), safety is not so resounding. However, this may be due more to comorbidity than age itself. The greatest amount of information available is with etanercept, as there are few studies—and those that exist are of poor quality—that assess the benefit-risk ratio of treatment with infliximab and adalimumab in the elderly.

Conflict of interest

The authors declare no conflict of interest.

Annex 1.

Search pattern	Results
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