

Original article

The impact of therapy with TNF-blockers on health-related quality of life in rheumatoid arthritis patients. A pilot study

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ABSTRACT

Introduction: The aim of this pilot study was to evaluate the initial response to 16 weeks of treatment with infliximab and etanercept of disease activity and quality of life in a cohort of 37 patients with established rheumatoid arthritis.

Patients and method: Patients were selected from the Unit of Rheumatology in Hospital Clínico San Cecilio from Granada, refractory to conventional treatment with disease modifying antirheumatic drugs. To assess the disease activity, Disease activity score (DAS28) was used and the measurement of quality of life was evaluated with the Spanish version of the SF-36 Health Survey (SF-36) and the RA-specific questionnaire QoL Scale (Quality of Life in Rheumatoid Arthritis).

Results: Preliminary results show a significant decrease in inflammatory activity of the disease and consequently in HRQL scores. The comparison with the general reference population shows a deviation well below average, especially in the "physical function" dimension with a rising response pattern in all dimensions. The correlation between specific scores (QoL-RA scale) and generic ones (SF-36) for HQ-treatment also showed significance, especially with the physical aggregate.

Discussion: An important limitation of the present study is the number of patients and the duration of the treatment; despite this, improvements in functional parameters and quality of life are evident and remain roughly stable since the first weeks of treatment. This allows us to continue the study and increase the number of patients.

Conclusions: The preliminary results obtained with TNF-blockers after 16 weeks of treatment in RA objectively show the effectiveness of these drugs and also the perception by the patients of the effect on their quality of life.

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Calidad de vida relacionada con la salud tras terapia anti-factor de necrosis tumoral alfa en pacientes con artritis reumatoide. Un estudio piloto

RESUMEN

Introducción: El objetivo de este estudio piloto ha sido valorar la respuesta inicial tras 16 semanas de tratamiento con infliximab y etanercept sobre la actividad de la enfermedad y la calidad de vida (CV), en una cohorte de 37 pacientes con artritis reumatoide establecida.

Pacientes y método: Los pacientes fueron seleccionados en el Servicio de Reumatología del Hospital Clínico San Cecilio de Granada, por ser refractarios al tratamiento convencional con fármacos antirreumáticos mo-

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dificadores de la enfermedad. Para evaluar la actividad de la enfermedad se utilizó el índice DAS28 (*Disease Activity Score*) y para CV, la versión española del Cuestionario de Salud SF-36 (*Health Survey SF-36*) y el cuestionario específico QoL-RA Scale (*Quality of Life in Rheumatoid Arthritis*).

Resultados: Los resultados preliminares muestran una disminución significativa en la actividad inflamatoria y consecuentemente en las puntuaciones de la CV. La comparación con la población general de referencia muestra una desviación muy por debajo de la media, especialmente en la dimensión «función física» con un patrón de respuesta ascendente en todas las dimensiones. La correlación entre puntuaciones específicas (QoL-RA Scale) y genéricas (SF-36) de CV postratamiento también mostraron significación, especialmente con el agregado físico.

Discusión: Consideramos una limitación importante del estudio el número de pacientes y el tiempo de evolución postratamiento. No obstante, las mejoras en los diferentes parámetros funcionales y de CV son objetivas y permanecen prácticamente estables desde las primeras semanas de tratamiento, lo que nos permitirá continuar el estudio y ampliar el número de pacientes.

Conclusiones: Los resultados preliminares obtenidos con anti-TNF alfa tras 16 semanas de tratamiento en artritis reumatoide muestran la efectividad de los fármacos objetivamente y subjetivamente según la percepción del paciente sobre su CV.

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Introduction

Rheumatoid arthritis (RA) implies an important change in people's quality of life. This fact has an explanation, as it is a disease whose main impact is generally not decreasing the patient's lifespan, but it is more about the more or less prolonged periods of disability that these patients face. In fact, rheumatic diseases are the first cause of disability in the young and elderly, and their main impact is precisely the fact that they do not let patients carry out their everyday activities.¹

Treatment has radically changed in the last few years due to the introduction of tumour necrosis factor (TNF) alpha drugs, which significantly reduce the inflammatory activity and improve physical function. As the quality of life improves, the number of patients limited in the working activities decreases,^{2,3} and although the disease does not disappear, its impact on the life of these people is lessened.

Health is a major critical factor in the quality of life of patients with chronic diseases.⁴ Determining the impact of the disease and/or its treatment on the life of people that suffer from it allows us to have an additional source of information apart from that of clinical data and laboratory tests.

The measurement of the quality of life permits us to assess medical treatment and provides us with a comparison of different therapeutic approaches, helping us to decide on the best.^{5,6}

There is also a new trend based on the need that patients themselves should share responsibilities regarding decisions that affect their health (covered by all current ethical codes). It is therefore necessary to question the patients, as objectively as possible, on what they think their quality of life is at a specific time of the evolutionary process of the disease affecting them, so that this can serve as a base for later assessment.⁷

This aim of this study was to assess the effects on disease activity and the quality of life after treatment with anti-TNF drugs for 16 weeks, during a pilot sample of patients diagnosed with RA, refractory to conventional treatment with disease modifying anti-rheumatic drugs^{8,9} and subsidiaries of anti-TNF biological treatment.

Patients and method

Sample

In this pilot study, through intentional random sampling, 37 patients were chosen that had been diagnosed with RA at the Rheumatology Department of the Hospital Clínico San Cecilio of Granada and still had persistent disease activity after having been

subjected to appropriate conventional treatment with disease-modifying anti-rheumatic drugs (DMARDs) for more than a year. The mean age was 49±13 (47±12 in males and 51±14 in females), with a range of 26 to 70 years. When the groups were divided in ages for later standardization of quality of life according to the reference Spanish population, we noticed that the largest group was 30 to 60 years (66%), with a mean age of 49.8 years, consistent with the greatest peaks of RA incidence (40–60 years). There were 26% more than 60 years old and only 8% less than 30 years old. A third of the patients were male and 58% had disease evolution longer than 5 years.

Procedure

The anti-TNF drugs used were infliximab and etanercept, given that there is no scientific evidence that endorses one drug over the other and, according to their technical data, both agents are indicated for RA.¹⁰ Infliximab was administered intravenously at a dose of 3 mg/kg, followed by additional doses at 2 and 6 weeks after the first and afterwards every 8 weeks. Etanercept was administered subcutaneously at the normal dose of 25 mg twice a week.

Information was collected twice (before and after treatment), separated by 16 weeks of treatment.

All the principles and recommendations for this type of studies were taken into account, according to all the rulings of the Ethics Committee and Clinical Trials of our hospital. This included always obtaining written informed consent from our patients for anti-TNF treatment.

Instruments

Disease activity was assessed with the Disease Activity Score 28 (DAS28) index.^{11,12} Its interpretation allows disease assessment (DAS28 < 3.2 indicates low activity and < 2.6, remission) and response to medical treatment (a change of DAS28 > 1.2 is considered a good response; 0.6 to 1.2, a moderate response; and < 0.6, no response).

The Spanish version of the generic questionnaire Health Survey SF-36 (SF-36)¹³ was used to measure the quality of life together with the specific questionnaire Quality of Life in Rheumatoid Arthritis (QoL-RA Scale).^{14,15} The SF-36 consists of 36 items that cover two areas: functional state and emotional well-being. The first is represented by the following measurements: physical function (10 items), social function (2 items), role limitations due to physical problems (4 items) and role limitations through emotional problems (3 items). The well-being area includes measurements for mental health (5 items), vitality (4 items) and pain (2 items). Finally, the general health assessment includes the measurement for perceived general health (5 items) and

Table 1
Clinical and laboratory variables used in the DAS28 index

Variables	Before treatment Mean±SD	After treatment Mean±SD	Difference before-after Mean±SD	P
VAS	7.38±1.25	3.25±1.51	4.13±1.61	.0001
NPJ	5.82±4.22	1.34±1.99	4.48±3.59	.0001
NSJ	2.76±2.28	0.28±0.60	2.48±2.11	.0001
ESR	40.16±17.68	17.68±12.73	22.48±16.65	.0001
CRP	2.67±2.61	0.68±0.80	1.98±2.69	.0001

CRP indicates C reactive protein; ESR, erythrocyte sedimentation rate; NPJ, number of painful joints; NSJ, number of swollen joints; SD, standard deviation; VAS, visual analogue scale.

Table 2
Disease activity and quality of life in RA

Variables	Before treatment Mean±SD	After treatment Mean±SD	Difference before-after Mean±SD	P
DAS 28	5.43±0.66	3.01±1.08	2.42±1.06	.0001
QoL-RA	3.00±0.77	6.91±1.31	-3.90±1.31	.0001
P. AGG SF-36	19.83±4.14	36.34±10.64	-16.50±10.79	.0001
M. AGG SF-36	27.15±11.37	47.63±9.19	-20.48±10.34	.0001

DAS28 indicates Disease Activity Score; M.AGG, Mental aggregate; P.AGG, Physical aggregate; QoL-RA, Quality of Life in Rheumatoid Arthritis; SD, Standard deviation; SF-36, Health Survey SF-36.

change of health during the time (1 item, which does not form part of the final score). The items are coded, aggregated and transformed in scale for each measurement starting from 0 (the worst state of health for this measurement) to 100 (the best state of health).

Perhaps SF-36 is currently the most commonly used generic measurement instrument in the world. It is also a self-completion instrument, translated and validated in Spain, which has population reference standards,¹³ as it has been given to a representative sample of the general population. The population standards can be used to assess quantitatively and qualitatively the benefit of an intervention, such as that of anti-TNF treatment in our rheumatic patient cohort, prior to standardisation of the SF-36 scores for the different age subgroups into which the sample was stratified (<30 years, from 30 to 60 years and >60 years).

The questionnaire was not designed to create an overall index; however, it allows for the calculation of two summary scores, the state of physical health and the state of mental health. The available software (Medical Outcomes Trust, 1995) was used to recode the items. The QoL-RA Scale, which is also a questionnaire specifically designed to globally assess the impact of RA on quality of life, is understood as the patient's ability to satisfy his or her needs. Published in English and simultaneously adapted to Spanish, it has 8 items (each one with a definition of the point considered), followed by a horizontal scale numbered between 1 (very bad) and 10 (excellent). The points questioned are: physical capability, pain, interaction with family and friends, help of family and friends, depression, anxiety, arthritis and health. It is a simple instrument whose validity has been shown in these patients.

The statistical analysis was carried out with the Statistical Package for the Social Sciences version 15.0 for Windows. Once the normality of the variables was tested in the study to assess the therapeutic effects of the medication on disease activity and quality of life, a comparison of means was performed using Student's t test for paired samples. The Pearson correlation coefficient was also used to correlate the quality of life scores.

Results

Table 1 and Table 2 present a summary of the mean scores obtained from the 37 patients with RA before starting the anti-TNF treatment (before treatment) and 16 weeks later (after treatment), as well as the difference between both measurements and the comparison of

means, indicating the statistical significance. Both tables gather the results for the clinical and laboratory variables, the disease activity assessed by the DAS28 index, the specific quality of life assessed by QoL-RA and the summary scores for generic quality of life, represented by physical and mental aggregates, valued through SF-36.

Figure presents our patients' standardised scores compared to the Spanish reference population for 45 to 54 years, as we consider this age range to have the majority of our sample. However, three age groups have been differentiated, to see all previous measurements of the quality of life profile and changes after treatment on the same graph. The increase was statistically significant in all the sub-scales, with there always being a rising improvement pattern, although with some differences according to the age group considered. Given that the same quality of life pattern is maintained in all the age groups, we present only one comparison graph of our patients with a general population of 45 to 54 years.

In Table 3, you can see the correlation coefficients between the mean quality of life scores assessed with specific QoL-RA and all the

Table 3
Correlation between the generic (SF-36) and specific (QoL-RA) quality of life scores before and after treatment

	BEFORE	AFTER
SF-36 AGGREGATES		
P. AGG	0.16	0.85***
M. AGG	0.48**	0.46**
SF-36 MEASUREMENTS		
PF	0.37*	0.84***
RP	-	0.64***
BP	0.22	0.83***
GH	0.23	0.74***
VT	0.44**	0.89***
SF	0.38*	0.74***
RE	0.28	0.32
MH	0.61***	0.77***

Pearson correlation and P-value coefficients between physical and mental aggregates and measurements of quality of life Questionnaire SF-36 with the specific QoL-RA. BP, Body pain; GH, general health; M. AGG, Mental aggregate; MH, mental health; P. AGG, Physical aggregate; PF, physical function; RE, Emotional role; SF, social function; VT, vitality; *: P<.050; **: P<.010; ***: P<.001.

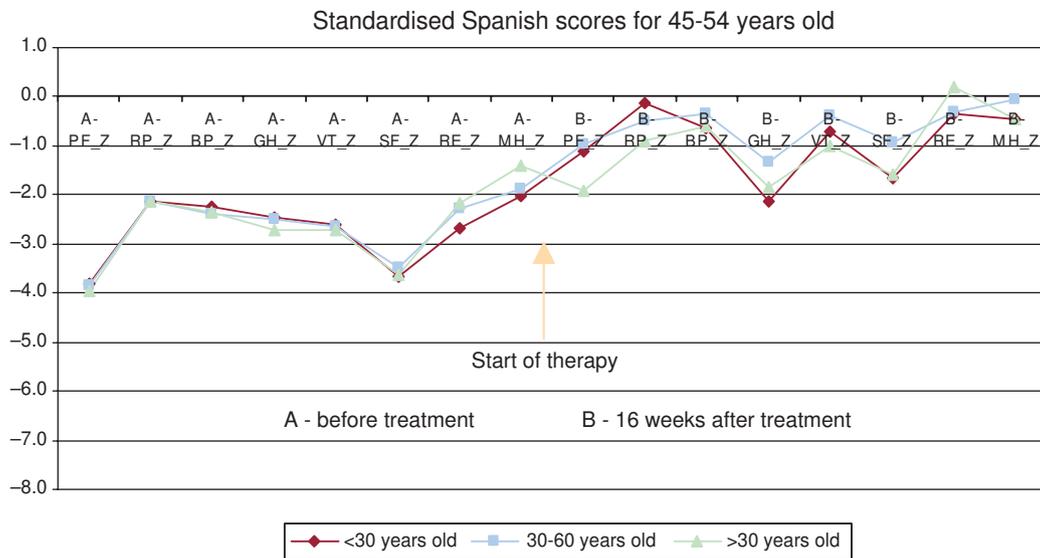


Figure. Standard SF-36 scores with respect with the Spanish reference population, before and 16 weeks after treatment. SF-36 measurements: BP indicates body pain; GH, general health; MH, mental health; PF, physical function; RE, role limitations due to emotional problems; RP, role limitations due to physical problems; SF, social function; VT, vitality. For each Z measurement: standard differences with respect to the Spanish population (value-mean reference/deviation reference).

measurements and sub-scales of generic quality of life, as well as the physical and mental aggregates assessed through SF-36.

Discussion

Different studies indicate that patients with RA have worse quality of life (in every way) than the general population and than patients with diseases considered more serious, such as heart attack, ulcerative colitis and systemic lupus erythematosus.¹⁶ The clinical activity level of the disease influences the quality of life. Consequently, patients with active disease have worse quality of life than those in remission.

Although many different measurement instruments have been developed to present RA activity and its improvement, we have opted for the DAS28 index, because it is the most commonly used in everyday clinical practice, as it combines information on the number of painful and swollen joints, general subjective patient assessment and acute phase reactants in just one formula.¹² Our results are in line with what has been reported in other studies on the efficiency of the drugs that block alpha TNF action. After 16 weeks of treatment, all indicative parameters of the active disease used to calculate the DAS28 index^{17,18} (Table 1 and Table 2) were significantly reduced. During this time interval, the majority of patients achieved the therapeutic aim according to the criteria of the European League against rheumatism,¹² with good response in 86.5% of patients and moderate in 8%. Remission occurred in 43.2% of patients, while 37.8% and 16.2% reached a moderate and low activity of the disease respectively.

According to the DAS28 index, disease activity after treatment decreased from 5.43 to 3.01 ($P<.001$), confirming an improvement in the disease (low activity < 3.2). The change experienced in the DAS28 index was 2.42 (Table 2), double what would be considered a good response to this disease¹² (good response > 1.2). These results coincide with those of the European study by Vander Cruyssen,¹ where anti-TNF treatment efficacy in patients with RA was assessed through the DAS28 index; it was found that 62% presented a DAS28 less than 3.2 and in up to 49.5%, the score was even lower than 2.85 in the long term.

The frequency of adverse reactions in our patients was similar to that described for this type of drugs¹⁹: local eczema in the injection area with etanercept in two cases and an allergic reaction to the infliximab infusion (urticaria) in one.

The scores obtained with the quality of life instruments complement the information on the effects produced by the anti-TNF therapy on disease activity change, with the psychological, social and physical effects being an important part of what the therapy additionally provides. Table 2 depicts the quality of life changes observed after 16 weeks of treatment ($P<.001$) with the specific QoL-RA instrument for patients with RA. We share with other authors²⁰ that low scores before starting anti-TNF treatment were preferably determined by pain and depressive symptoms and patients saw the effect of the new anti-TNF medication as something beneficial, which was reflected in their quality of life.

With regards to scores obtained from the generic SF-36 quality of life questionnaire, the comparison of before and after treatment means in all measurements resulted statistically significant ($P<.001$). In Table 2, you can see the summary scores of the physical and mental aggregates.

Our results corroborate that the decrease in RA activity, as a response to treatment with anti-TNF drugs, is associated with a significant change in the quality of life assessed with SF-36,^{21,17} despite the number of patients in the sample ($n=37$). However, although the limited number of patients could be considered an important limitation together with the follow-up period of only 16 weeks, it was a pilot study to assess the initial response to treatment. It will consequently allow us to continue with the therapy given the general good tolerance and absence of complications, as well as increasing the sample by recruiting new patients.

It has been shown that the improvement obtained in the different functional parameters and the quality of life can be made objective and remain practically stable from the first few weeks of treatment. We therefore consider that these changes represent a new hope for patients with RA, as recently reported by Gülfe et al. We also feel they entail a clear impact on direct and indirect costs derived from the disease, which should help us in our position of prescribing favourable cost-effective treatments.

When comparing our patients' pretreatment SD (standard deviation) (Figure A) with the general population of similar age ranges, we observe a homogeneous behaviour in the three age groups, with SDs that are much more negative for the "physical function" measurement, compared to the reference population group. However, it should be pointed out that role limitations for physical tasks have deviations closer to the general population than the rest of the measurements, which are also negative, but more moderate than those of physical function.

Mean patient SDs after treatment (Figure B), compared with the reference group considered, clearly reflect the differences through age groups. We should highlight the recuperation of the "physical function" and "physical role" measurement, especially in younger patients, that reaches the base line. This also suggests that treatment is particularly beneficial for them. In our sample, all pretreatment SDs are negative and are found to be much lower than the reference values. In addition, although they follow the rising pattern of recovery after treatment, only some reach or overtake these values. In the case of the "emotional role" subscale in the more elderly, who are those who generally suffer from a longer disease evolution, these individuals perceive changes in response to the treatment with greater satisfaction. This is also reflected in the "general health" perception, which overtakes that of the younger ones, but in all cases is maintained below the baseline.

Some studies that refer to significant improvement in disease activity reflected by the laboratory parameters and acute phase reactants report patients who do not subjectively perceive increases in their quality of life, according to the specific QoL-RA scale.²² In our case, all patients significantly improved not only in clinical symptoms but in laboratory parameters (Table 1), perceiving an overall increase in their quality of life, although with differences according to the SF-36 considered (Figure 1). However, when correlating QoL-RA scores with the different SF-36 measurements and with physical and mental aggregates, we observe that the correlation for emotional role is not significant either before or after treatment. A possible explanation would be that the questions included in this SF-36 measurement do not have a correlation with the specific QoL-RA scale, as the patient is not questioned on the disturbances that emotional problems can have on work and other type of activities. Treatment response generally shows a high correlation between the scores of quality of life of both instruments (Table 3). The physical aggregate also shows a high correlation coefficient after treatment, but it is not significant before it. Again, it is difficult to associate various questions related to the physical functions in a generic way, with only one closely-related RA question. Perhaps the patient may associate the gain in quality of life after treatment especially with the physical aspects that are the most limiting; this would consequently justify the high correlation between both scores after the treatment. Following up our patients and the possibility of increasing our sample would allow us to clarify some points and establish a profile of quality of life according to age and possibly gender, to implement psychological support strategies if necessary.

Finally, we consider that treatment with anti-TNF drugs represents a therapeutic option of great interest in preventing disability and thus being able to maintain the autonomy of RA-affected patients for as long as possible, as it is one of the rheumatic diseases with the worst prognosis.

Conflict of interest

The authors declare no conflict of interest.

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