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FINAL DEGREE PROJECT

RELATIONSHIP OF PSYCHOSOMATIC DISORDERS (anxiety, depression) AND DIFFICULT-TO-TREAT RHEUMATHOID ARTHRITIS: A PILOT STUDY.

RHEUMATOLOGY DEPARTMENT

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Vull donar les gràcies a la Dra Marta Valls Roc, per ensenyar-me tant, per la seva ajuda i guia durant aquests dos mesos i, sobretot, per fer que si em quedava algun dubte sobre quina especialitat escollir, ja no me'n quedi cap.

Moltes gràcies Marta, ho he disfrutat molt.

Ha estat un plaer.

A sa meva família, especialment a nes meus pares, per donar-me sempre es suport i ses eines necessàries per ser aquí on sóc.

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ABSTRACT

Background: Despite advances and efficacy of rheumatoid arthritis treatments, there is still an amount of **difficult-to-treat** patients, with persistence of signs and symptoms of disease activity (DAS 28 ≥ 3.2) and failure to treatment.

Not all the regrowths of these patients involve active inflammation (**true refractory**), because there is a subgroup without inflammation (**false refractory**). In these patients the cause of refractoriness is not well known (probably the comorbidities that they have are related, and one of them can be **psychosomatic disorders**).

Meanwhile the cause remains unclear, this subgroup of patients follows inadequate treatments assuming an impact on the patient's health and for the socioeconomic system.

Objectives: The objective of our study is to see that false refractory patients have greater anxiety and depression than true refractory patients.

Design: cross-sectional analytic study

Methods: Refractory rheumatoid arthritis patients who attend consultations for 1 year will be collected. We will pass to them some questionnaires to assess depression and anxiety and health status (HADS, SF 36) and refractoriness (DAS 28, RAPID 3).

An articular ultrasound and determination of ADAs will be performed in order to differentiate between true and false refractory patients.

Participants: Patients with persistent signs and symptoms active disease (DAS 28 ≥ 3.2), failure to second bDMARD, and impossibility to reduce glucocorticoids.

Key words: *refractory rheumatoid arthritis (RRA), depression and anxiety, true refractory patients, false refractory patients, DAS 28, HADS, SF 36, RAPID 3*.

ABBREVIATIONS

RA: Rheumatoid Arthritis

RRA: Refractory Rheumatoid Arthritis

PD: Psychosomatic Disorders

DMARDs: Disease-Modifying Antirheumatic Drugs

S DMARDs: Synthetic Disease-Modifying Antirheumatic Drugs

B DMARDs: Biological Disease-Modifying Antirheumatic Drugs

NSAIDs: Non-steroidal anti-inflammatory drugs

DAS 28: Disease Activity Score-28

RAPID 3: Routine Assessment of Patient Index Data 3

SDAI: Simplified Disease Activity Index

CDAI: Clinical Disease Activity Index

HAQ-DI: Health Assessment Questionnaire-Disability Index

HADS: Hospital Anxiety and Depression Scale

SF 36: 36-item Short-Form Health Survey

ESR: Erythrocyte sedimentation rate

CRP: C-reactive protein

EULAR: European League Against Rheumatism

ACR: American College of Rheumatology

RF: Rheumatoid Factor

aUS: Articular Ultrasound

ADA: Antidrug antibody

APR: Acute phase reactants

DSM-V: Diagnostic and Statistical Manual of Mental Disorders

MDD: Major Depressive Disorder

1.INTRODUCTION

RHEUMATOID ARTHRITIS

DEFINITION

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory disease that primarily targets synovial tissues. The etiology of RA is unknown, although is believed to appear due to the action of environmental agents (infections, smoking, etc.) on a predisposed genetic field (carriers of the histocompatibility antigen DR4).

The patients manifest an *additive symmetric polyarthritis* (pain and joint inflammation) specially of the wrists and hands, affecting the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints, accompanied with joint stiffness, deformity and muscle weakness.

Furthermore, they exhibit some systemic features such as: fatigue, low-grade fevers, anemia, and elevations of acute phase reactants (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) (1).

The systemic inflammation is believed to be responsive for a variety of extraarticular manifestations and coexistent comorbid conditions including **cardiovascular disease, osteoporosis, cognitive dysfunction, psychiatric disease (depression) and cancer**.

Both have an extraordinary influence regarding the *prognosis* and *quality of life* of patients, as well as with other outcomes, such as mortality, hospitalization and work disability (2).

Figure 1 Ulnar deviation of the 3rd, 4th and 5th fingers and swelling of the metacarpophalangeal (MCP joints (1)

EPIDEMIOLOGY

RA is a worldwide chronic disease with a global prevalence of between 0.2% and 1.2%, and higher frequency in women than in men (3:1 ratio). In Spain, an accumulated prevalence of RA of 0.5% (95% confidence interval [CI], 0.2-0.8) was estimated. It has an annual incidence of 8.3 cases per 100.00 adults aged 16 and older (3).

CLINICAL COURSE

In 70% of cases, RA follows a progressive course, with fluctuations in severity. In the rest it can have an intermittent course, in which the outbreaks of arthritis are followed by remissions of variable duration. This fluctuating course, partly due to the disease itself and partly to the treatments, makes it necessary to frequently carry out measures of the process that reveal the state of the disease at a given time (activity).

For the evaluation of the disease activity, the following tests are used: Disease Activity Score-28 (**DAS 28**), Simplified Disease Activity Index (**SDAI**) and Clinical Disease Activity Index (**CDAI**) and the Health Assessment Questionnaire-Disability Index (**HAQ-DI**) (1).

COMORBIDITIES IN RA

The comorbidities associated with a higher mortality in RA patients are cardiovascular and respiratory diseases, neoplasms and **depression** (4).

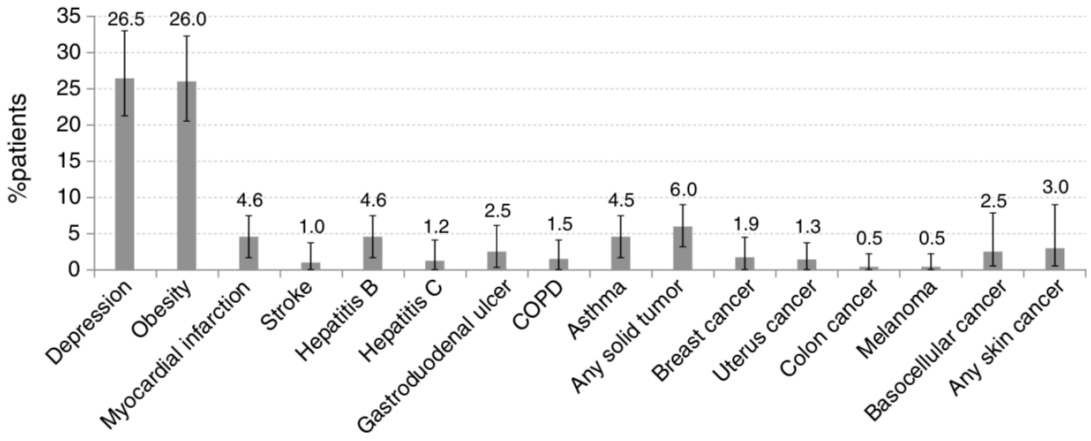


Figure 2 Prevalence of comorbidities in Spanish patients with RA. Abbreviations: COPD, chronic obstructive pulmonary disease (5).

Depression and anxiety's prevalences in RA are high from the moment of diagnosis, being the most frequent disorders of the psychological sphere of the disease. A large number of patients experience clinically significant depressive symptoms (the results of a systematic review suggest that prevalence estimated is between 14% and 48%; this rate can vary among countries and according to the screening tool), but do not meet the complete diagnoses criteria for **major depressive disorder** (MDD) (6).

From a clinical point of view, **depression and anxiety** are associated with increases in pain, inflammation and disability. They seem to **decrease patient's adherence to medical treatment** and are associated with **an increase in disability**, a **worsening of the quality of life** and **lower rates of disease remission and treatment response**.

DIAGNOSIS

Although it is a clinical diagnosis, based on the symptoms and signs and the findings in the complementary tests, the **classification criteria of the American College of Rheumatology (ACR) of 1987** and/or the **criteria of the European League Against Rheumatism (EULAR) / ACR 2010** (*ANNEX 1, page 32)* are used as diagnostic criteria (1).

SOCIO-HEALTH IMPACT OF RA

RA affects many aspects of the individual's life, such as physical condition (**chronic pain** and **disability** affect the performance of activities of daily living) and mental health**,** economic well-being, relationships with caregivers, family members and friends.

The socioeconomic impact is due to an important consumption of resources, related to the disease and associated disability.

And the economic impact of RA is especially important due to the use of high-cost drugs, such as new biologics drugs, and the limited resources of current healthcare systems. The costs increase with disease activity. **Consequently, not only obtaining a rapid remission of the disease significantly improves the quality of life of the patient, but it also produces a significant reduction of indirect costs** (7)**.**

PROGNOSIS

Not only the prognosis of RA influences the patient (interferes in the adaptation to the social, economic and emotional changes that the disease entails) but it also influences

the treatment (determines the choice of therapeutic strategy and the assessment of benefit risk).

Some patients with a severe prognosis may benefit from more aggressive treatments at the onset of the disease. For this reason, is important to determine the prognosis, which depends on different factors (1).

PROGNOSTIC FACTORS OF SEVERE DISEASE
- Age - Female gender - Number of swollen joints - Rheumatoid factor (RF) and citrullinated anti-peptide antibodies (ACPA) at high titles - Active smoking - Active disease - Presence of elevated acute phase reactants (ESR and CRP) - Early onset of erosions - Degree of initial disability

Table 1 Main factors of poor prognosis in RA

TREATMENT

The treatment of RA is based on the control of the manifestations and consequences of the disease, including the control of inflammation, structural sequelae and its comorbidities.

The actual treatment strategy is called “treatment strategy up to the objective” or “***treat to target***” (T2T). It is based on the need to be more ambitious in the therapeutic objective, trying to achieve the remission of the disease as soon as possible and making frequent evaluations.

The delay in treatment has been associated with progression of structural damage, so **early treatment with** *disease modifying antirheumatic drugs* (**DMARDs)** is important within what is known as the "*therapeutic window*." In this phase of the disease, the therapeutic intervention is able to modify the outcome of the disease.

DMARDs can be divided into synthetic and biological: **synthetic DMARDs** are a group of drugs with different mechanisms of action and toxicities that are used in RA to stop inflammation and prevent the outcome of the disease in all aspects. *Methotrexate* is the most used sDMARD in the treatment of RA; **biological DMARDs** are molecules that inhibit key therapeutic targets in the pathogenesis of the disease (4).

Therapeutics include the sequential administration of **sDMARDs**, initially including *methotrexate*, escalating thereafter to the use of **bDMARDs** (*TNF and IL-6 receptor inhibitors, rituximab, abatacept, and the most recently Janus kinase inhibitors*).

There is an algorithm based on the 2016 EULAR recommendations on RA management (8) *(ANNEX 2, page 33).*

Also, a parallel use of non-steroidal anti-inflammatory drugs (**NSAIDs)** and judicious use of **glucocorticoids** is a common practice.

Therapeutics should be adjusted based on formally assessed, intercurrent disease activity levels, to seek the lowest level of disease activity or remission.

Given the complexity of RA and the multiple existing treatments, the rheumatologist must be the specialist responsible for the management of the disease, in which a multidisciplinary approach should be a desirable option.

The overall management of RA includes patient health education, the application of psychosocial interventions, the implementation of measures to obtain adequate rest combined with physical exercise adapted to the patient, as well as dietary and nutritional advice (4).

Long term outcomes have improved remarkably in the last decade, despite there is a group of patients with **difficult-to-treat disease**.

REFRACTORY RHEUMATOID ARTHRITIS

INTRODUCTION

Refractory Rheumatoid Arthritis (RRA) is defined as "*an area of unmet clinical need*" (9).

The actual rheumatology literature (EULAR recommendations and ACR guidelines on the management of RA) is focused basically on early phases of RA and on

pharmacological management. This is related with the effectiveness of pharmacological treatments at early stages of RA, so this has led to the belief that RRA is a condition of the past, but it is a reality despite all the actual therapies, because a **significant proportion of patients remains symptomatic after a several cycles of treatment**, which makes them difficult-to-treat.

DEFINITION. WHAT DOES IT MEAN RRA?

Nowadays, there is not a consensus in the definition for RRA. Because of that, an online survey was made and distributed through the European rheumatologists in order to know what they consider to be RRA (*ANNEX 3, page* 34). And the results showed a wide variety of concepts, but **active disease, failure to DMARD treatment and inability to taper glucocorticoids** were considered the main characteristics.

So, therefore, the definition we take in this project for RRA is: patients with RA who **continue (persists) having signs and symptoms** that suggest inflammatory **disease activity** (**DAS 28 ≥ 3.2**) despite the treatment with multiple DMARDs (conventional synthetic and **at least two biological**), and **impossibility of reduce the dose of glucocorticoids** (10).

The choice of this cut-off regarding bDMARDs was arbitrary, because there is a lack of trials with the inclusion criterion of having failed at least two bDMARDs.

Also, it is important to know that the meaning of refractoriness is not always a synonymous of inflammation. **Many patients with active disease are not, or not only, due to inflammatory activity. And that is because in more advanced phases different factors could interfere in different measure** (11).

WHY IS RRA IMPORTANT?

In RRA, the drug treatment management is affected by a variety of factors. These factors make the treatment of these patients quite difficult.

As the contribution of the different factors in the RRA is unknown, the decisions and steps of the treatment of the patients are based on trial and error (9).

While the influence of these factors is not known and the appropriate treatment is not found, patients continue to suffer signs and symptoms, which affect their quality of life, and indirectly, the socio-health cost.

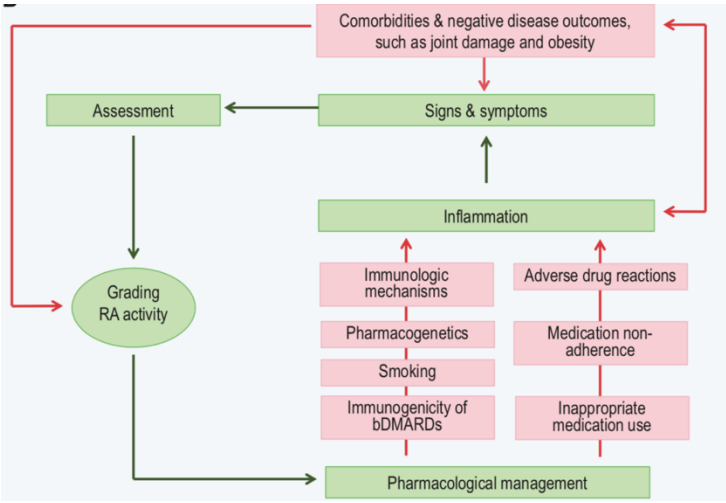


Figure 3 Drug management cycle. The factors (in red) can contribute to RRA.

PREDICTORS OF REFRACTORY COURSE

The baseline factors that are associated with a later refractory course and bDMARDs refractory disease include **age and gender**, **disease duration**, **disease activity, tobacco and obesity**, **number of comorbidities, delay in treatment** (12) (13).

PREVALENCE

It is difficult to say what the prevalence is, because it depends on the definition.

According to the definition we caught for this project, the estimated prevalence is between **5-20%** (10).

COMORBIDITIES IN RRA

RRA patients suffer from a variety of comorbidities. The most frequent ones are **hypertension**, **cardiovascular**, **respiratory** and **gastro-intestinal diseases** (14).

CAUSES OF REFRACTORINESS

The factors that made the RA difficult-to-treat can be classified in:

1. **Immunological characteristics** of each patient that result in persistence of active inflammation in joints (*synovitis*) seen by articular ultrasound (**aUS**) (15).

2. **Drug ineffectiveness**: includes drug intolerance, non-adherence, adverse drug reactions and **pharmacogenetic features**, like the presence of antidrug antibodies (**ADAs**) in blood test (16).
3. **Interfering comorbidities** and/or other factors (17).

Then, this leads to the differentiation between **three types of refractory patients**:

- The first group are patients who, despite everything, fail to control the disease and have persistent **inflammation [1]**. These patients enter into the **intrinsic refractory** group.
- In the second one, there are the patients who do not respond to the drug, either through intolerances, non-adhesions or because of pharmacogenetics features (ADAs) **[2]**. These patients are in the **pharmacological (PK) refractory** group.
- And in the third one, there are patients who do not respond to treatment, but not because of the presence of inflammation or problems with the drug apparently, and that is why it is not well known why they are refractory. So, it is believed that the comorbidities they have may play a **key role on the refractoriness, interfering with the disease and making it difficult to control**. These patients are in the group that we will call as **false refractory [3]**.

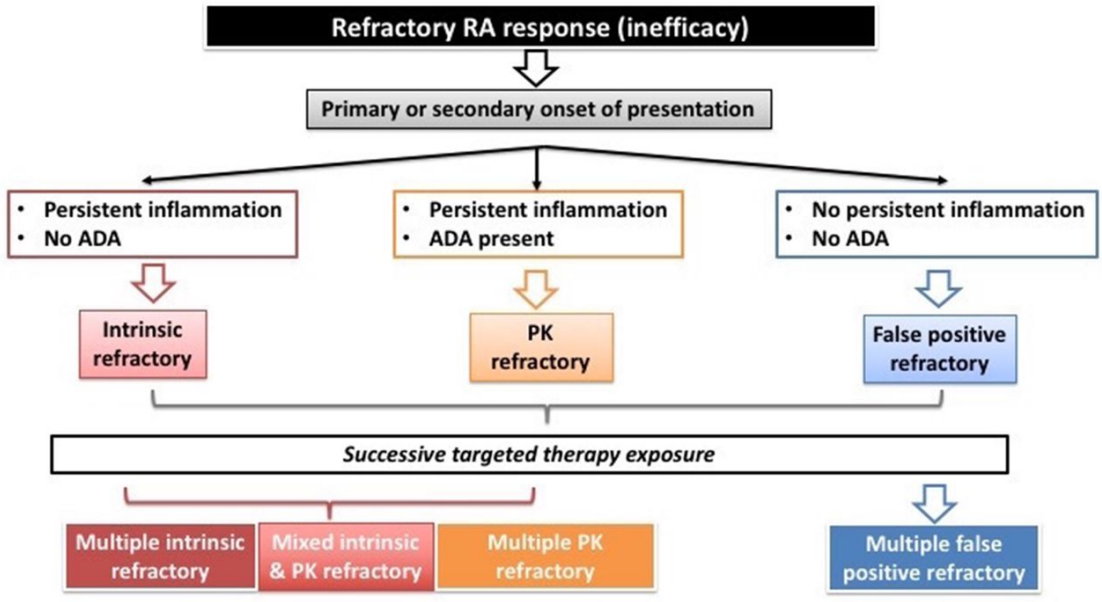


Figure 4 Schematic picture of the RRA classification (16)

To simplify, we will classify these patients into two large groups, one with **true refractory disease and the others with false refractory disease.**

Into the group of **true refractory patients,** are included the groups 1st and 2nd (**intrinsic and PK refractory**). These patients do not respond to the drug, either due to the characteristics of the disease (inflammation) or due to problems with the drug itself.

And **false refractory patients** are formed by the 3rd group (**false refractory**). In this group, the cause of the refractoriness is not exactly known, because these patients have no inflammation and no problems with the treatment, but there are some factors of non-inflammatory refractoriness that are probably related like **comorbidities** (**depression and anxiety**, fibromyalgia, arthrosis), **extraarticular manifestations** (pneumonia, dry syndrome), **patient expectations** and **psychosocial/laboral aspects** (17).

Because the lack of knowledge in this group, in this project we are going to focus on **false refractory patients**.

The idea is to see if there are differences in depression and anxiety between true and false refractory patients, **in order to observe if depression and anxiety would have an important role in the group of the false ones**.

TREATMENT

Currently, there is no consensus or recommendation (in EULAR recommendations or ACR guidelines) on the treatment of RRA. So, at the moment, the treatment is done under the criteria of the patient's rheumatologist.

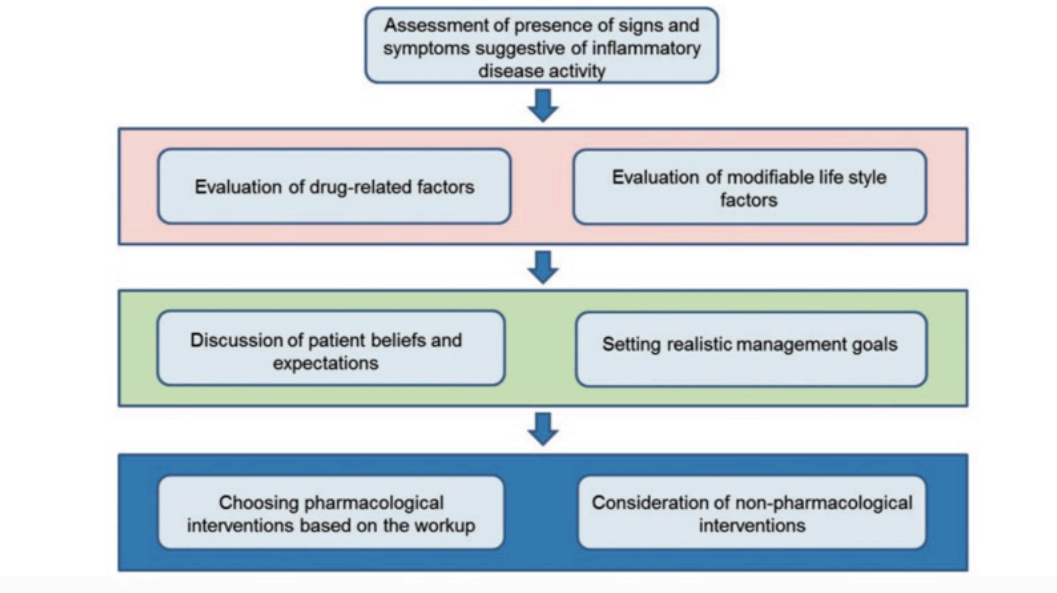


Figure 5 Management Approach to RRA patients (9)

PSYCHOSOMATIC DISORDERS: DEPRESSION AND ANXIETY

Psychosomatic disorders are currently known as *Psychological factors that influence other medical conditions* in **DSM-V** (*Diagnostic and Statistical Manual of Mental Disorders*). The term is used to refer when there are one or more significant psychological or behavioral factors that adversely affect a medical condition and increase the risk of suffering, death or disability (18) *(ANNEX 4, page 35).*

Many different psychological factors that adversely influence medical conditions have been demonstrated like symptoms of **depression** or **anxiety**, stressful life events, personality traits, maladaptive health behaviors such as denial of symptoms or poor adherence to medical recommendations.

Depression is a mental disorder characterized by the presence of sadness, loss of interest or pleasure, feelings of guilty or lack of self-esteem, sleep or appetite disorders, sensation of tiredness and lack of concentration. It can become chronic or recurrent and significantly hinder work performance and the ability to cope with daily life (19).

Anxiety disorders are characterized by intense fear and/or excessive worries that are difficult to control. They are multifocal (in relation to finances, family, health and the future) and are typically accompanied by other nonspecific psychological and physical

symptoms like fatigue, irritability or muscle tension. These disorders generate significant discomfort and affect the normal functioning of the person (20).

Anxiety and depression may accompany somatic symptom disorders. The somatic component adds complexity and causes greater severity, functional impairment and even refractoriness to traditional treatments (18).

RELATIONSHIP BETWEEN RA AND DEPRESSION

As already mentioned, it is well known that **patients with RA are more predisposed to suffer from depression**. RA implies the impact of the diagnosis of a chronic disease without cure, loss of social roles and employment due to disease and disability, and adverse effects of treatment.

There is literature that talks about the inflammatory hypothesis that links the systemic inflammation in RA and its effect on the brain structures involved in depression. Inflammatory cytokines (mainly **IL-6**) that circulate systemically, through different neuroendocrine pathways, affect areas of the brain linked to the production of depression. Although the mechanism by which it is produced is not well understood, it is believed that cytokines may also cause depression through hyperactivation of the *hypothalamic-pituitary-adrenal* (HPA) axis and dysregulation of the HPA axis has been associated with psychopathologies (depression, panic disorder and anxiety) (21) (22).

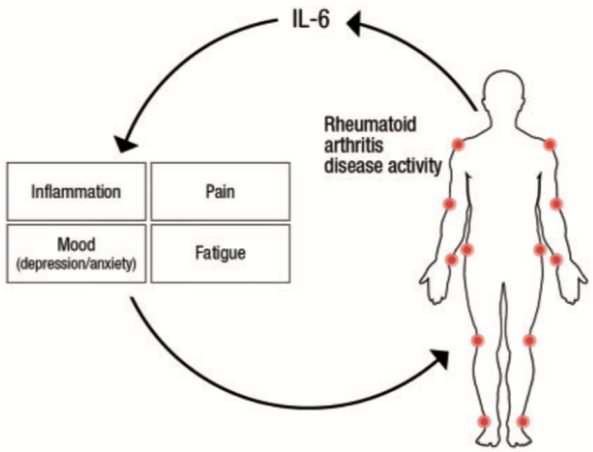


Figure 6 Picture of the interaction between pain, fatigue and mental state (mood)

On the other way, a possible **bidirectional relationship between depression and RA** has been postulated, in which the first would predispose to the development of RA.

It is known that depression significantly influences the course of RA, increasing the risk of regrowths and decreased remission, although the mechanism by which central inflammation in depression can induce systemic inflammation and result in autoimmune disease, is still being studied (23).

2. JUSTIFICATION

The causes of refractoriness in the group of patients with false RRA are not exactly known. What we know is that there are different related factors and one of them may be comorbidities such as depression and anxiety.

If we do not know what causes refractoriness, we cannot adequately treat patients, using perhaps inappropriate therapeutic strategies with new biological drugs, which means an increase in socioeconomic cost. Furthermore, and perhaps the most important thing, this can cause an alteration on the physical condition (because each time a new drug is started, there is greater risk to produce truly refractory pathology) and mental health (the burden of accepting the failure of another treatment and assuming the start of a new one) of the patients.

Maybe, these patients would benefit more from other pharmacological or non-pharmacological treatments, like the referral to a psychologist or psychiatrist for the optimal treatment of anxiety and/or depression, and therefore, improve the course of the RA.

So, our goal is to see if patients with false refractory rheumatoid arthritis have elevated prevalence of depression and anxiety, compared to the true refractory ones.

The proposal to carry out this objective is a cross-sectional study to evaluate disease activity and mental health status (prevalence of psychosomatic disorders, depression and anxiety) in the RRA patients and their possible relationship with the false refractory ones.

3.HYPOTHESIS

The hypothesis of the study is that patients with false refractory rheumatoid arthritis have high prevalence of anxiety and depression, compared to the patients with true refractory disease.

4.OBJECTIVE

The objective of the study is to see if there is a high prevalence of anxiety and depression in the patients with false refractory rheumatoid arthritis. **We want to see if there are differences in the proportion of depression and anxiety with the true refractory patients.**

5.METHODOLOGY

Study Design

We will carry out a **cross-sectional analytic study** to assess the mental health status (PD, depression and anxiety) and disease activity of the patients.

The **study population** are the patients with RRA of the Hospital Dr Josep Trueta (Girona) and the Hospital Santa Caterina (Salt, Girona).

To do the study, I will count with the help of rheumatologists of Hospital Dr Josep Trueta and Santa Caterina in Girona. They will pass some pre-selected questionnaires to the patients that come to the follow-up visit.

When a patient (previously identified as refractory for the rheumatologist) arrives to the health center and is being visited, the rheumatologist of the service will be able to print **4 tests** to give to the patients:

- Two to assess the activity of the disease (**DAS 28**, **RAPID 3**) (*ANNEX 5 and 6, pages 36-37*)
- Two to evaluate anxiety and depression and health status (**HADS**, **SF 36**) [*ANNEX 7 (page 39) and 8 (page 46)]*

In advance, patients will be explained in what the study consists of and an **informed consent** will be delivered to all of them.

Also, in order to differentiate between true and false RRA patients, an **articular ultrasound** (**aUS**) will be performed to them (to evaluate whether there is inflammation or not, **intrinsic refractoriness**) and a **determination of ADAs in serum** will also be required (to evaluate if there is antidrug antibodies, **PK refractoriness**). Then, according to the results, we will classify the patients into two groups:

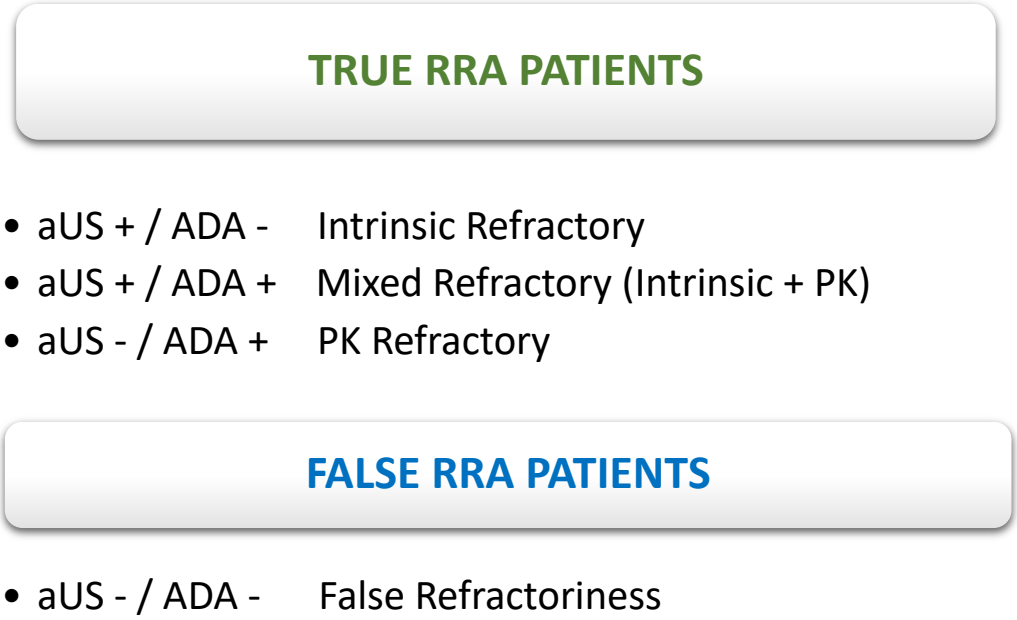


Figure 7 Classification of the patients according to the results of the aUS and ADAs determination

We will try to disturb the patient as little as possible, so the ADAs will be assessed in the routine blood test (before the visit, according to the daily clinical practice), and the questionnaires and the articular ultrasound will be performed in the same review visit, so that the patient does not have to go to an extra one.

With all the information of the questionnaires, explorations and baseline data, at the end of the visit, the rheumatologists will fill in the **data collection notebook** (*ANNEX 9, page 48*) and save it to the database of the rheumatology service.

	False refractory patients	True refractory patients	Total
With depression and anxiety			
Without depression and anxiety			
Total			

Table 2 Summary table for the results (proportion's table)

Study subjects: Inclusion and Exclusion criteria

The patients will be collected according to the following criteria:

Inclusion criteria:

- Patients > 18 years old
- Patients with RRA according to the definition we have provided at the beginning of the project (presence of symptoms, DAS 28 $\geq$ 3,2, failure to a 2nd bDMARD and impossibility to reduce the use of glucocorticoids)
- Patients with signed informed consent
- Controlled patients at the Dr Josep Trueta and Santa Caterina Hospital

Exclusion criteria:

- Age < 18 years
- Any demographic characteristic or pathology that the patient presents and that a medical criterion contraindicates the collection of data

Sampling and sample size

The **sample** will be made up of patients with RRA who attend hospital appointments. Patients who come during the period of **one year** will be collected. The period of time can be extended to two years if it is necessary.

It will be a non-probabilistic, **consecutive sampling**. We will pick up the patients (with inclusion criteria) who come progressively to rheumatology consultations for review (over 1 year, extendable to 2 years).

We do not have **sample size**, since it is a pilot study because there is not previous data of the prevalence of PD in false RRA patients.

For the performance of statistical calculations, a minimum of 30 participants are required.

To find out the approximate number of refractory patients between the two hospitals, we addressed via email to the *Secretaria Tècnica* (*Gerència Territorial Girona; Institut Català de la Salut, Departament de Salut, Generalitat de Catalunya*) of the Hospital Dr. Josep Trueta.

We explained to them that we were carrying out a final degree project to evaluate the affected patients with refractory rheumatoid arthritis and we wanted to know if they could provide to us the total number of patients that had been codified as rheumatoid arthritis between the two hospitals, in order to calculate approximately the number of refractory patients.

Since we asked for the total number of patients (data without confidential information) they accepted our request.

Associated to the email, they gave us an excel with the codes of patients diagnosed with rheumatoid arthritis between 2009 and 2017 according to *Classificació Internacional de Malalties* **CIM 9** (code 714.0) and between 2018 and 2019 according to **CIM 10** (codes M05 and M06). These are different patients with diagnosis.

According to CIM-10, there were a total of 623 patients with RA. If the prevalence of RRA oscillates between 5-20%, we would have between 31 and 125 refractory

patients. With the CIM-9, there were a total of 226 patients with RA, so we would have between 11 and 45 refractory patients.

Considering the two codifying systems and the prevalence of the RRA, we will collect probably between 42 and 170 refractory patients in our study.

Variables

Independent variables

The independent variables of the study will be anxiety and depression (psychosomatic disorders). They will be evaluated through *Hospital Anxiety and Depression Scale* (**HADS**). They are quite subjective variables and their symptoms can overlap and may hinder the diagnosis, but he HADS test has good internal validity and consistency in order to evaluate both (24).

We also will use the 36-item Short-Form Health Survey (**SF 36).** It assesses physical, mental, social, emotional and general health components (25) (26).

These are considered as discrete quantitative variables, according to the HADS and SF 36 results. In this study we will categorize them to be qualitative dichotomous variables.

In HADS, patients with scores greater than or equal to 11 will be considered as cases of depression and/or anxiety, and those with lower scores will not (patients with or without depression and/or anxiety).

We are going to do the same with the results of SF 36. Patients with scores greater than 50 will be considered with good health status, and patients with scores below 50 with poor health status (patients with or without good health status).

Dependent variables

The dependent variable of the study will be the refractoriness (moderate disease activity) of the RA.

The disease activity will be assessed by **DAS 28** (Disease Activity Score 28 joint counts), that measures disease activity through clinical and laboratory measures (4) and **RAPID**

3 (Routine Assessment of Patient Index Data 3) that also values the quality of life (27). These are considered as continue quantitative variables according to the results of DAS 28 and RAPID 3. We will do the same as with the dependent variables and categorize them to be qualitative dichotomous variables.

In DAS 28, patients with scores ≥ 3.2 (moderate activity) are going to be considered as refractory. Patients with lower scores are not going to be considered refractory.

In RAPID 3, patients with scores ≥ 6,1 (moderate activity) are going to be considered refractory, and the ones with lower scores as no refractory.

Covariables

We will take as covariates the risk profiling factors of refractoriness.

So, the covariables of the study will be:

- Age and gender
- Tobacco (current smoking) and obesity (IMC)
- Disease duration
- Number of comorbidities (fibromyalgia and arthrosis)
- Extraarticular manifestations (pneumonia, dry syndrome)
- Delay in treatment (date of diagnosis and start date of treatment).

All these variables will be recollected in the data collection notebook, and they will be assessed with a multivariate analyses.

Measuring instruments

The following table summarizes the scoring methods of each questionnaire and how we will interpret the results to classify the patients into the *table 3*.

Name of the test	**Scoring method**	**Interpretation of the Results**
HADS	14 questions, 7 assess anxiety and 7 depression. Each subscale scores from 0 to 21 and each question scores from 0 to 3.	Patients with a score **between 11-21 are considered**

<table>
<tr><td></td><td>Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)</td><td>a case (depression and/or anxiety). Patients with a score below 10, are considered to have no depression and/or anxiety.</td></tr>
<tr><td>SF 36</td><td>Measures 8 dimensions (physical, mental, social, emotional and general health components). The scores of each of the 8 dimensions range between values 0 and 100 (100 being a result that indicates optimal health and 0 would reflect a very bad state of health).</td><td>Scores above 50 indicate better health status.

Scores below 50 indicates worse health status.</td></tr>
<tr><td>RAPID 3</td><td>Evaluates activity of the disease perceived by the patient and the degree of response evaluating clinical measures.

<table><tr><th>REMISSION</th><th>LOW ACTIVITY</th><th>MODERATE ACTIVITY</th><th>HIGH ACTIVITY</th></tr><tr><td>0 - 3</td><td>3,01 - 6</td><td>6,01 - 12</td><td>> 12</td></tr></table></td><td>Patients with ≥ 6,01 will be considered as refractory.</td></tr>
<tr><td>DAS 28</td><td>Index statistically derived from the count of swollen and painful joints, the ESR and the overall assessment of the patient, and which has been modified to be used with 28 joints (DAS28).

<table><tr><th>REMISSION</th><th>LOW ACTIVITY</th><th>MODERATE ACTIVITY</th><th>HIGH ACTIVITY</th></tr><tr><td>< 2.6</td><td>2.6 - 3.2</td><td>3.2 - 5.1</td><td>> 5.1</td></tr></table></td><td>Patients with ≥3.2 are considered as refractory.</td></tr>
</table>

Data collection notebook

For data collection, we need to know which patients have inclusion criteria and which exclusion criteria.

Then, the next step, the patients included in the inclusion criteria, will be explained about this study and then they will sign the informed consent document.

Data that will be collected during the visit is:

- Identification code of the patient
- Informed consent (*ANNEX 10, page 50*)
- Inclusion criteria
- Age and sex
- Tobacco, IMC
- Clinic history of RA: date of diagnosis, date start of treatment, values of RF and ACPA, presence of radiological erosions
- Current treatment: NSAIDs, glucocorticoids, DMARDs
- Comorbidities and extraarticular manifestations (previous history of depression or anxiety, fibromyalgia, arthrosis, pneumonia, dry syndrome)
- Clinical evaluation: number of painful joints, number of swollen joints, visual analog scale of pain, of general state and of the doctor's assessment
- Activity Index: DAS 28, RAPID 3
- aUS report
- Tests for depression and anxiety and health's status: HADS, SF 36
- ADAs and acute phase reactants: ESR (mm/h), CRP (mg/L)

All the information will be stored in the rheumatology service database.

With these data, we will divide all the RRA patients between true and false refractory and see the prevalence of depression and anxiety in both groups.

6.STATISTICAL ANALYSES

Descriptive Analyses

We will summarize the dependent variables, using proportions expressed in percentages. The same will be done for the qualitative covariates.

We will summarize the quantitative covariates using means and the standard deviation when they are represented continuously in a distribution graphic and by using medians when they are discrete variables.

Bivariate Interference

We will contrast the difference in proportions of the dependent variables, and of the qualitative covariates by means of Chi-square and Fisher's exact test.

We will contrast the difference of means and means of the covariates by means of the student T and the Mann-Whitney U.

Multivariate Analyses

We will evaluate the refractoriness of RA using logistic regressions where the response variables will be the indexes of evaluation of the disease activity (DAS28, RAPID 3).

The explanatory variable of interest will be psychosomatic disorders (anxiety and depression), adjusting for covariates.

7.WORK PLAN

We will recruit all the patients with difficult-to-treat RA that comes to the consults of rheumatology, during the period of one year.

Health care personnel include the rheumatologists of the hospital Josep Trueta and Santa Caterina as co-investigators of the study and one statistician to analyze the results.

-STAGE 1: coordination and redaction of study protocol

1.1 Scientific research and protocol elaboration

The first step is the elaboration of the protocol. It is carried out through the approach of a study and the identification of the appropriate study variables to answer the

hypothesis that has been formulated. Therefore, an extensive literature research is carried out. Then, the study methodology is established.

1.2 Ethical approval (CEIC)

In the second step, the protocol must be evaluated by Comitè d'Ètica i d'Investigació Clínica (CEIC). It is carried out before starting the study.

1.3 Initial coordination meeting

Step three will involve organizational meetings in order to coordinate all the rheumatologists of the Hospital Dr Josep Trueta and Santa Caterina.

1.4 Chronogram

After step three, a chronogram will be made up, after the mutual agreement of all the parties involved.

It is estimated that this phase will last approximately 5 months.

- STAGE 2: sample collection, visits, and data collection

2.1 Recruitment

This phase consists in recruiting during a year the patients who attend the consultations, meet the inclusion criteria and have signed the informed consent.

2.2 Data collection

This phase is based in collecting the baseline data, the results of the questionnaires and the explorations realized to the participants. The rheumatologists will collect the information in each visit, in the data collection notebook.

2.3 Coordination meetings

The principal investigator will meet the co-investigators in order to assess that the protocol is well executed and to determine if they need to modify some procedures.

The duration of this phase is estimated to be 1 year, and may be extended to 2 if necessary.

-STAGE 3: statistical analysis and interpretation of the results

3.1 Statistical analysis

This phase will consist of data processing and statistical analysis, and is expected for 3 months. This phase will involve the investigators and the statistician.

3.2 Description of the results

After the statistical analysis is completed, results will be analyzed and the possible conclusions will be drawn.

-STAGE 4: publication of results

4.1 Final article elaboration

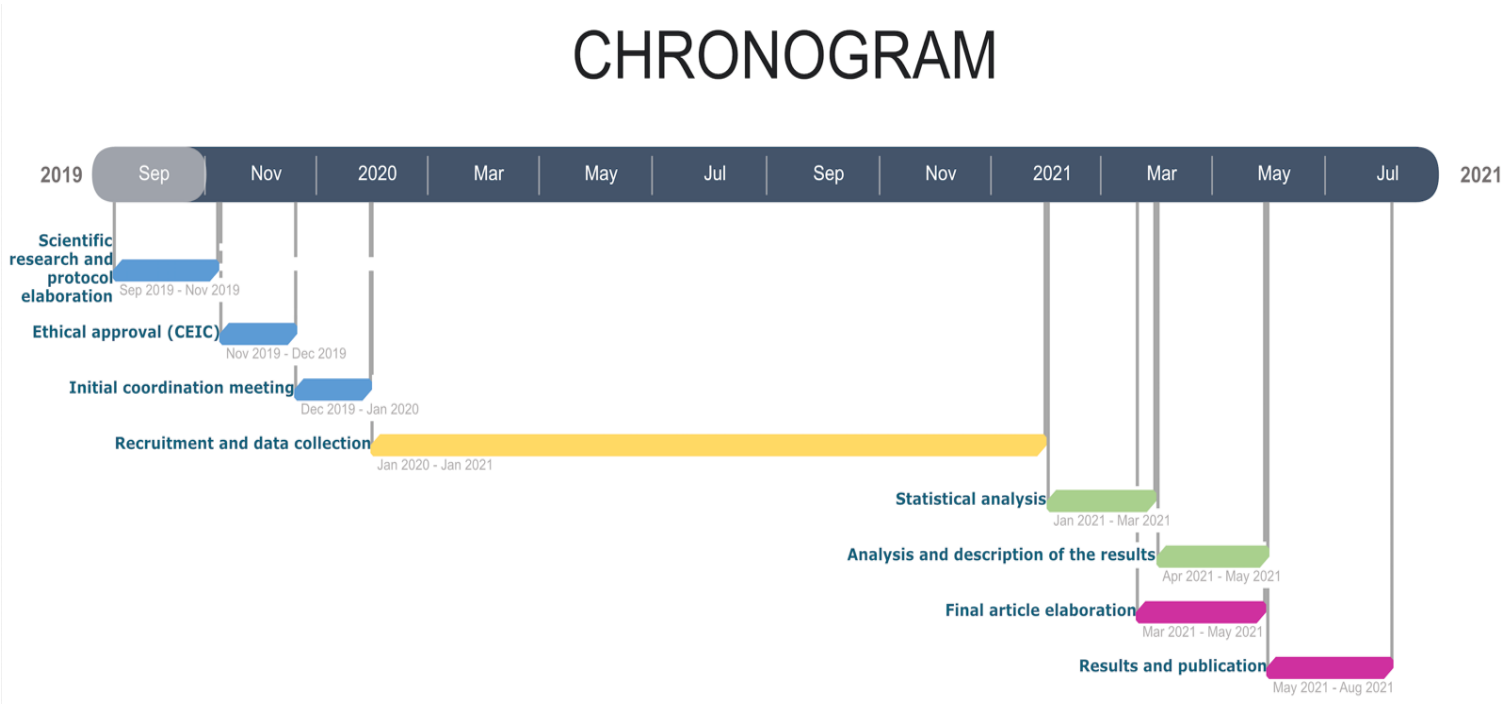
During the last phase, the results will be prepared for publication and is expected to take 3 months.

This will be done by the investigators.

4.2 Results publication

Finally, the results will be summarized in format of scientific papers and will be sent to medical journals for their publication.

-CHRONOGRAM



8. ETHICAL ASPECTS

The project will be evaluated by the **Comitè d'Ètica i d'Investigació Clínica (CEIC)** of the Hospital Dr Josep Trueta (Girona) and Hospital Santa Caterina (Salt, Girona).

Participants will be informed about the explorations that will be carried out and they will be asked for **informed consent** before the inclusion into the project.

The principles of human experimentation will be respected, according to the **Hèlsinki Agreement**.

In addition, access to the information obtained from any analysis performed is guaranteed.

The rules of **confidentiality** will be respected, participants will be informed according to **Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales** (28)**,** that they could be subject to automated processing and the rights of the study participants to consult, modify or delete their personal data from the file.

There is no **conflict of interests** regarding the publication of this paper.

9. LIMITATIONS OF THE STUDY

- The most important limitation of the study is the two-way relationship (*reverse causality*) that exist between RA and depression. RA predisposes to depression, and depression can be a risk factor for developing RA. This will be a problem when evaluating the possible relationship between depression and anxiety with the refractoriness. For this reason, we are going to ask patients about previous episodes of depression and anxiety.
- Another limitation of the study is that by performing a consecutive sampling we may not obtain a representative sample of the population (selection bias). To try to reduce it, we will collect patients during a period of 1 year, extendable to 2 years, to ensure to the maximum that we catch all the possible patients (usually they go every 2-6 months to revision).

- Also, we are aware that the data we are evaluating has high subjectivity (quality of life, depression and anxiety, pain, ...). To try to evaluate these variables as well as possible and avoid information bias, we will pass several tests to the patients, to assess the variables with the most specific tool (test) for each one.
- There are some variables that can confuse the results (risk profiling factors of refractoriness). As this is a pilot study, we are not going to exclude the patients with these conditions, but we will take into account when analyzing the data.

10. BUDGET

EXPENSES		
RESQUESTED BUDGET		
		COSTS (€)
PERSONAL EXPENSES -Rheumatologists		**200€ x patient**
	Subtotal	8.400€ - 34.000€
EXECUTIVE EXPENSES -Blood test (ADAs determination) -Articular Ultrasound -Data management -Statistician		**72€ x patient** **20€ x patient** **400h/30€** **100h/35€**
	Subtotal	3.929 € - 15.705€
PUBLICATION AND DISEMINATION EXPENSES -Scientific publications -Scientific publication (x2, both protocol and results publication) -Travel transportation, accommodation, meetings		**1500€** **1500€** **5000€**
	Subtotal	8.000 €
	Approximate Total Budget	**20.329€ - 57.705€**

11. IMPACT OF THE PROJECT IN THE SNS

As it is a pilot study, we don't know exactly what impact it would have at the economic level of the *Sistema Nacional de Salud* (SNS). But, if patients with false refractoriness treated with biological drugs, can really improve the course of the disease and health status with non-pharmacological therapies or appropriate drugs (for example, for the treatment of depression and anxiety, with surely lower cost) is possible that it would have a beneficial impact, both for patients and the socio-health system.

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13.ANNEXES

ANEX 1: Diagnostic criteria of Rheumatoid Arthritis

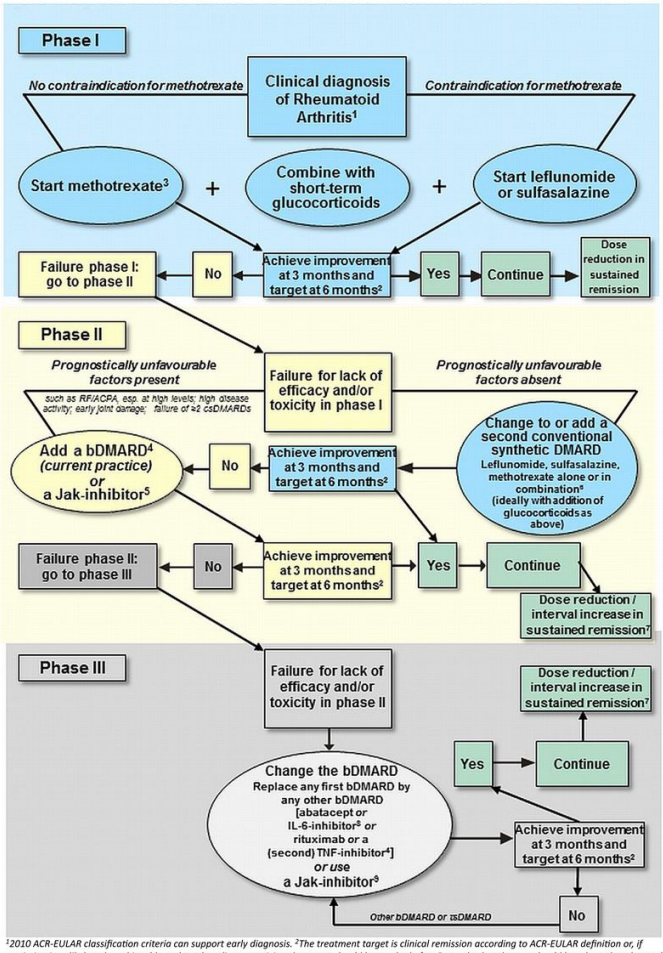
Criterios de la American Rheumatism Association 1987 para la clasificación de artritis reumatoide (AR)	
Criterio	Definición
1. Rigidez matutina	Rigidez matutina de al menos 1 h de duración
2. Artritis de 3 o más áreas articulares	Al menos 3 áreas articulares presentan simultáneamente tumefacción de partes blandas o derrame observados por un médico
3. Artritis de las articulaciones de las manos	Tumefacción en al menos una articulación: muñeca, MCP o IFP
4. Artritis simétrica	Afectación simultánea de las mismas áreas articulares en los 2 lados del cuerpo
5. Nódulos reumatoides	Nódulos subcutáneos sobre prominencias óseas o superficies extensoras o en regiones yuxtaarticulares observados por un médico
6. Factor reumatoide sérico	Demostración de aumento anormal del factor reumatoide sérico
7. Cambios radiológicos	Cambios típicos de AR en la radiografía de manos y muñecas, que deben incluir erosiones o descalcificación ósea localizada en las articulaciones afectadas

Un paciente será clasificado como AR si satisface al menos 4 de los 7 criterios. Los criterios 1 a 4 deben estar presentes durante al menos 6 semanas.
IFP: interfalángicas proximales; MCF: metacarpofalángicas.

Criterios de la American Rheumatism Association/European League Against Rheumatism (ACR/EULAR) 2010 para la clasificación de artritis reumatoide	
Población diana:	
1. Sinovitis (inflamación) confirmada en al menos 1 articulación	
2. Sinovitis no explicada por otra enfermedad	
Se precisa un índice ≥ 6/10 para la clasificación de AR definida	
Afectación articular[a]	
1 articulación grande	0
2-10 articulaciones grandes	1
1-3 articulaciones pequeñas (con o sin afectación de articulaciones grandes)	2
4-10 articulaciones pequeñas (con o sin afectación de articulaciones grandes)	3
> 10 articulaciones (al menos una pequeña)[b]	5
Serología[c]	
ACPA y FR ambos negativos	0
ACPA o FR ambos positivos (títulos bajos)	2
ACPA o FR ambos positivos (títulos altos)	3
Reactantes de fase aguda	
PCR y VSG normales	0
PCR o VSG elevados	1
Duración de los síntomas	
< 6 semanas	0
≥ 6 semanas	1

[a]La afectación articular se refiere a cualquier articulación dolorosa o inflamada en la exploración, que puede ser confirmada por pruebas de imagen.
Las articulaciones interfalángicas distales, primeras carpometacarpianas y primeras metatarsofalángicas son excluidas de la valoración.
– Articulaciones grandes: hombros, codos, caderas, rodillas y tobillos.
– Articulaciones pequeñas: metacarpofalángicas, interfalángicas proximales, 2.ª a 5.ª metatarsofalángicas, interfalángicas del pulgar y muñecas.
[b]En esta categoría, al menos una articulación afectada debe ser pequeña. Puede incluir combinaciones de grandes y pequeñas, así como otras articulaciones en distintas localizaciones (temporomandibular, acromioclavicular, esternoclavicular, etc.).
[c]Se consideran títulos bajos valores ≤ 3 veces mayores que el límite superior de la normalidad. Títulos altos, valores > 3 veces el límite superior de la normalidad. En caso de que solo conozcamos si el factor reumatoide es positivo o negativo (y no su titulación), un resultado positivo se puntuará como positivo-bajo.
ACPA: anticuerpos antipéptidos citrulinados; PCR: proteína C reactiva; VSG: velocidad de sedimentación globular.

ANEX 2: Therapeutic algorithm of Rheumatoid Arthritis

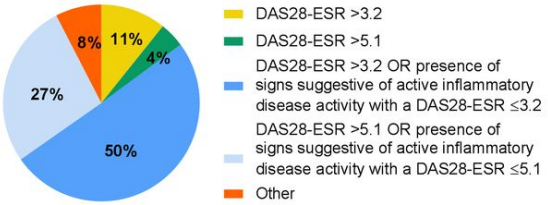


[1]2010 ACR-EULAR classification criteria can support early diagnosis. [2]The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [3-7]Methotrexate should be part of the first treatment strategy[3]; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. [4]TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6-inhibitors, or rituximab; in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages. [5]Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). [6]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. [7]Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. [8]Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [9]Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown.

ACPA, anticitrullinated protein antibody; ACR, American College of Rheumatology; bDMARD, biological DMARD; bsDMARD, biosimilar DMARDs; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs; EMA, European Medicines Agency; FDA, Food and Drug Administration; IL, interleukin; MTX, methotrexate; RF, rheumatoid factor; TNF, tumour necrosis factor; tsDMARDs, targeted synthetic DMARDs.

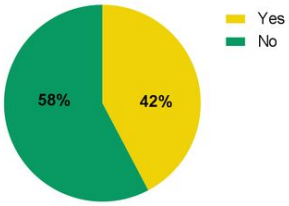
ANEX 3: Results of international survey to the rheumatologists

A. What should be the definition for not well-controlled disease in the definition of difficult-to-treat RA?



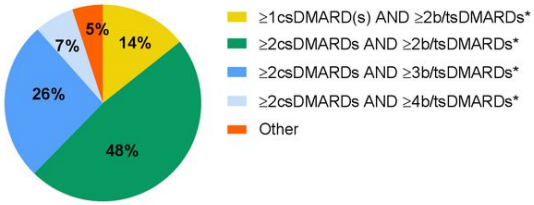
Total responses = 409

B. Would you include fatigue in the definition of not well-controlled disease?



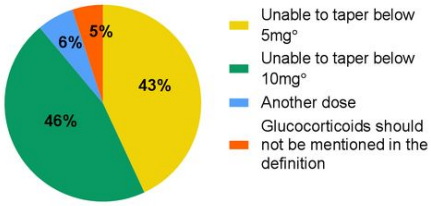
Total responses = 396

C. Which and how many antirheumatic drugs should at least be tried with insufficient effect for the definition of difficult-to-treat RA?



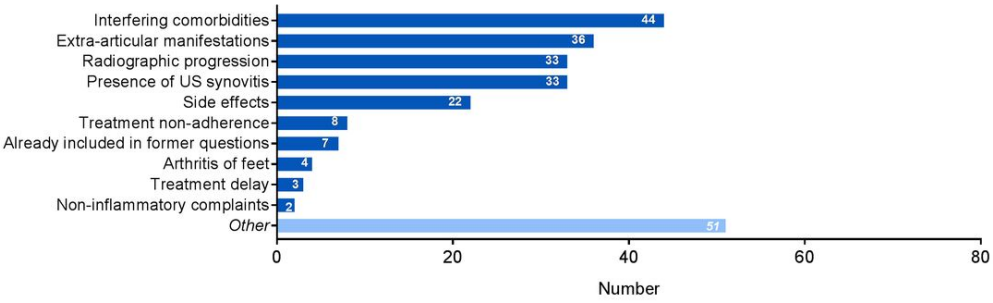
Total responses = 398

D. Treatment with glucocorticoids should be mentioned in the criteria for difficult-to-treat RA as follows:



Total responses = 397

E. Additional characteristics of difficult-to-treat RA



ANEX 4: Diagnostic criteria of Psychosomatic Disorders

The **diagnostic criteria** are:

A. Presence of a **medical symptom or condition** (other than a mental disorder).

B. **Psychological or behavioral factors** that negatively affect the medical condition in one of the following ways:

1. The factors have influenced the course of the medical condition as evidenced by a close temporal association between psychological factors and the development or exacerbation or delay in the recovery of the medical condition.
2. The factors interfere in the treatment of the medical condition.
3. The factors constitute other well established risks to the health of the individual.
4. The factors influence the underlying pathophysiology, because they precipitate or exacerbate the symptoms, or need medical assistance.

C. The psychological and behavioral factors of Criterion B are not better explained by another mental disorder (ex, panic disorder, major depression disorder, post-traumatic stress disorder).

Specify the severity:

Mild: Increases medical risk (ex, inconsistency with compliance with antihypertensive treatment).

Moderate: The underlying medical condition worsens (ex, anxiety that aggravates asthma).

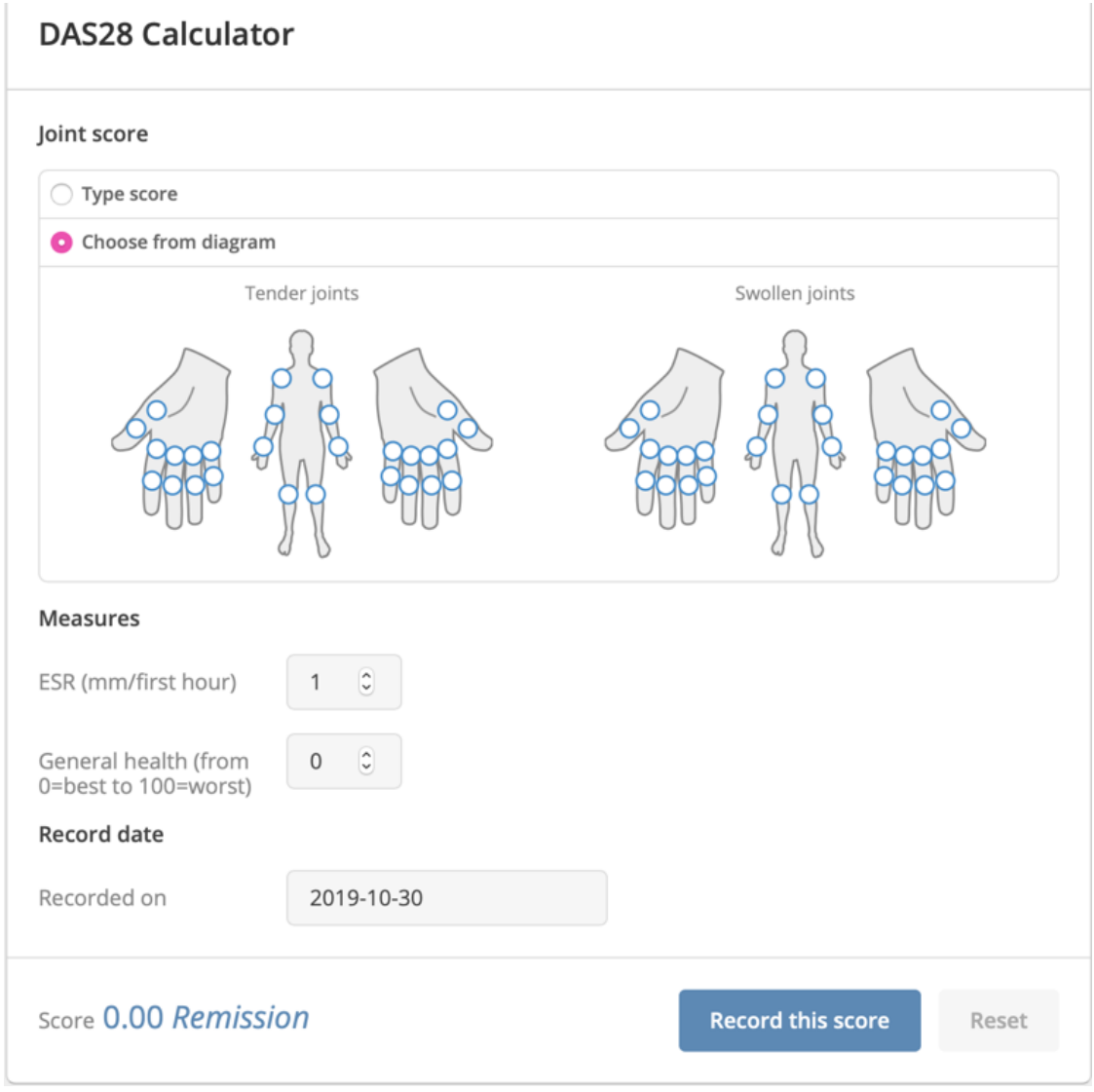
Serious: It results in hospitalization or visit the emergency department.

Extreme: Produces a significant, life-threatening risk (e.g., ignoring symptoms of a heart attack).

ANEX 5: DAS 28

DAS 28: Index statistically derived from the count of swollen and painful joints, the ESR and the overall assessment of the patient, and which has been modified to be used with 28 joints (DAS28).

REMISSION	LOW ACTIVITY	MODERATE ACTIVITY	HIGH ACTIVITY
< 2.6	2.6 - 3.2	3.2 - 5.1	> 5.1



ANEX 6: RAPID 3

CUESTIONARIO DE EVALUACIÓN DEL ESTADO DE SALUD (R808-NP2-Spanish)

El siguiente cuestionario incluye información no disponible en análisis de sangre, rayos X o de ninguna otra fuente más que Ud. Por favor intente responder cada pregunta aun cuando crea que no se relaciona con Ud. en este momento. No hay respuestas correctas o incorrectas. Por favor responda lo que Ud. piense o sienta. Muchas gracias.

SÓLO PARA USO MÉDICO

1.a/ FN (0-10):

1=0.3 16=5.3
2=0.7 17=5.7
3=1.0 18=6.0
4=1.3 19=6.3
5=1.7 20=6.7
6=2.0 21=7.0
7=2.3 22=7.3
8=2.7 23=7.7
9=3.0 24=8.0
10=3.3 25=8.3
11=3.7 26=8.7
12=4.0 27=9.0
13=4.3 28=9.3
14=4.7 29=9.7
15=5.0 30=10

2.PN (0-10):

4.PTGL (0-10):

RAPID 3 (0-30)

Cat:
HS = >12
MS = 6.1-12
LS = 3.1-6
R = <3

1. Nos interesa saber de qué manera su enfermedad afecta sus capacidades y habilidades para realizar actividades de la vida diaria. Por favor marque (√) la respuesta que mejor describa su capacidad para hacer las cosas o sus habilidades usuales (habituales) DURANTE LA SEMANA PASADA:

DURANTE LA SEMANA PASADA, ¿pudo Usted...	Sin **NINGUNA** Dificultad	Con **ALGO** de Dificultad	Con **MUCHA** Dificultad	**IMPOSIBLE** de Hacer
a. ¿Vestirse solo(a), incluyendo amarrarse (atarse) los cordones de los zapatos, abotonarse (abrocharse) y desabotonarse (desabrocharse) la ropa?	0	1	2	3
b. ¿Acostarse y levantarse de la cama?	0	1	2	3
c. ¿Levantar una taza o un vaso lleno para llevárselo a la boca?	0	1	2	3
d. ¿Caminar fuera de casa, sobre un terreno plano?	0	1	2	3
e. ¿Lavarse y secarse el cuerpo?	0	1	2	3
f. ¿Agacharse para recoger ropa o algo del piso o el suelo?	0	1	2	3
g. ¿Abrir y cerrar las llaves del agua (grifos, canillas)?	0	1	2	3
h. ¿Subir (meterse) y bajar (salir) de un automóvil?	0	1	2	3
i. ¿Caminar 3 kilometros?	0	1	2	3
j. ¿Participar en juegos y deportes como Ud. quisiera?	0	1	2	3
k. ¿Dormir bien por las noches y tener un sueño reparador?	0	1.1	2.2	3.3
l. ¿Controlar sus nervios o ansiedad?	0	1.1	2.2	3.3
m. ¿Controlar sus sentimientos de depresión o melancolía?	0	1.1	2.2	3.3

2. Cuánto DOLOR ha tenido por su enfermedad DURANTE LA ÚLTIMA SEMANA? Por favor marque con una X en la línea de abajo para indicar cuánto dolor ha tenido:

SIN NINGÚN DOLOR ○ EL PEOR DOLOR QUE SE PUEDA IMAGINAR
0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10

3. Por favor indique la intensidad del dolor que ha tenido el día de hoy en cada una de las articulaciones abajo mencionadas. Coloque una X en el número que describa la intensidad de su dolor.

	Nada	Leve	Moderado	Severo/fuerte		Nada	Leve	Moderado	Severo/fuerte
a. DEDOS MANO IZQ	☐ 0	☐ 1	☐ 2	☐ 3	i. DEDOS MANO DER	☐ 0	☐ 1	☐ 2	☐ 3
b. MUÑECA IZQ.	☐ 0	☐ 1	☐ 2	☐ 3	j. MUÑECA DER	☐ 0	☐ 1	☐ 2	☐ 3
c. CODO IZQ	☐ 0	☐ 1	☐ 2	☐ 3	k. CODO DERECHO	☐ 0	☐ 1	☐ 2	☐ 3
d. HOMBRO IZQ	☐ 0	☐ 1	☐ 2	☐ 3	l. HOMBRO DER.	☐ 0	☐ 1	☐ 2	☐ 3
e. CADERA IZQ	☐ 0	☐ 1	☐ 2	☐ 3	m. CADERA DER	☐ 0	☐ 1	☐ 2	☐ 3
f. RODILLA IZQ	☐ 0	☐ 1	☐ 2	☐ 3	n. RODILLA DER	☐ 0	☐ 1	☐ 2	☐ 3
g. TOBILLO IZQ	☐ 0	☐ 1	☐ 2	☐ 3	o. TOBILLO DER	☐ 0	☐ 1	☐ 2	☐ 3
h. DEDOS PIE IZQ	☐ 0	☐ 1	☐ 2	☐ 3	p. DEDOS PIE DER	☐ 0	☐ 1	☐ 2	☐ 3
q. CUELLO	☐ 0	☐ 1	☐ 2	☐ 3	r. ESPALDA	☐ 0	☐ 1	☐ 2	☐ 3

4. Considerando todas las formas en las que su artritis o enfermedad le afecta, por favor marque con una X en la línea de abajo lo que mejor describa cómo se siente en este momento:

MUY BIEN ○ MUY MAL
0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10

POR FAVOR VOLTEE LA PÁGINA

En 2008, Pincus y cols.[1] desarrollaron el RAPID3 (Routine Assessment of Patient Index Data 3): es un índice de la actividad de la artritis reumatoide que incluye tres medidas autorreportadas por el paciente: la función física, el dolor y la evaluación global de la enfermedad por el paciente.

Es un índice sencillo, puede ser completado en la sala de espera por el paciente, es rápido (se contesta en tan sólo 5-10 minutos) y de cálculo simple.

En 2011, Maldonado y cols.[2] validaron el cuestionario RAPID3 en versión española en pacientes con artritis reumatoide temprana y establecida, evaluaron su correlación con otros índices de actividad y medidas de evaluación y determinaron el tiempo utilizado para completar y calcular el cuestionario.

INTERPRETACIÓN

Los rangos de puntuación resultantes se interpretan:

- De 0 a 3: Remisión de la enfermedad
- De 3,01 a 6: Baja actividad de la enfermedad
- De 6,01 a 12: Moderada actividad de la enfermedad
- Más de 12: Alta actividad de la enfermedad

REMISSION	LOW ACTIVITY	MODERATE ACTIVITY	HIGH ACTIVITY
0 - 3	3,01 - 6	6,01 - 12	> 12

ANEX 7: SF 36

CUESTIONARIO DE SALUD SF-36

Marque una sola respuesta

1) En general, usted diría que su salud es:

a. Excelente
b. Muy buena
c. Buena
d. Regular
e. Mala

2) ¿Cómo diría que es su salud actual, comparada con la de hace un año?

a. Mucho mejor ahora que hace un año
b. Algo mejor ahora que hace un año
c. Más o menos igual que hace un año
d. Algo peor ahora que hace un año
e. Mucho peor ahora que hace un año

Las siguientes preguntas se refieren a actividades o cosas que usted podría hacer en un día normal

3) Su salud actual, ¿le limita para hacer esfuerzos intensos, tales como correr, levantar objetos pesados, o participar en deportes agotadores?

a. Sí , me limita mucho
b. Sí, me limita un poco
c. No, no me limita nada

4) Su salud actual, ¿le limita para hacer esfuerzos moderados, como mover una mesa, pasar la aspiradora, jugar a los bolos o caminar más de una hora?

a. Sí , me limita mucho
b. Sí, me limita un poco
c. No, no me limita nada

5) Su salud actual, ¿le limita para coger o llevar la bolsa de la compra?

a. Sí , me limita mucho
b. Sí, me limita un poco
c. No, no me limita nada

6) Su salud actual, ¿le limita para subir varios pisos por la escalera?

a. Sí , me limita mucho
b. Sí, me limita un poco
c. No, no me limita nada

7) Su salud actual, ¿le limita para subir un solo piso por la escalera?

a. Sí , me limita mucho
b. Sí, me limita un poco
c. No, no me limita nada

8) Su salud actual, ¿le limita para agacharse o arrodillarse?

a. Sí , me limita mucho
b. Sí, me limita un poco
c. No, no me limita nada

9) Su salud actual, ¿le limita para caminar un kilómetro o más?

a. Sí , me limita mucho
b. Sí, me limita un poco
c. No, no me limita nada

10) Su salud actual, ¿le limita para caminar varias manzanas (varios centenares de metros)?

a. Sí , me limita mucho
b. Sí, me limita un poco
c. No, no me limita nada

11) Su salud actual, ¿le limita para caminar una sola manzana (unos 100 metros)?

a. Sí , me limita mucho
b. Sí, me limita un poco
c. No, no me limita nada

12) Su salud actual, ¿le limita para bañarse o vestirse por sí mismo?

a. Sí , me limita mucho
b. Sí, me limita un poco
c. No, no me limita nada

<u>Las siguientes preguntas se refieren a problemas en su trabajo o en sus actividades diarias</u>

13) Durante las últimas 4 semanas, ¿tuvo que reducir el tiempo dedicado al trabajo o a sus actividades cotidianas a causa de su salud física?

a. Sí
b. No

14) Durante las últimas 4 semanas, ¿hizo menos de lo que hubiera querido hacer, a causa de su salud física?

a. Sí
b. No

15) Durante las últimas 4 semanas, ¿tuvo que dejar de hacer algunas tareas en su trabajo o en sus actividades cotidianas, a causa de su salud física?

a. Sí
b. No

16) Durante las últimas 4 semanas, ¿tuvo dificultad para hacer su trabajo o sus actividades cotidianas (por ejemplo, le costó más de lo normal), a causa de su salud física?

a. Sí
b. No

17) Durante las últimas 4 semanas, ¿tuvo que reducir el tiempo dedicado al trabajo o a sus actividades cotidianas a causa de algún problema emocional (como estar triste, deprimido, o nervioso)?

a. Sí
a. No

18) Durante las últimas 4 semanas, ¿hizo menos de lo que hubiera querido hacer a causa de algún problema emocional (como estar triste, deprimido, o nervioso)?

a. Sí
b. No

19) Durante las últimas 4 semanas, ¿no hizo su trabajo o sus actividades cotidianas tan cuidadosamente como de costumbre, a causa de algún problema emocional (como estar triste, deprimido, o nervioso)?

a. Sí
c. No

20) Durante las últimas 4 semanas, ¿hasta qué punto su salud física o los problemas emocionales han dificultado sus actividades sociales habituales con la familia, los amigos, los vecinos u otras personas?

a. Nada
b. Un poco
c. Regular
d. Bastante
e. Mucho

21) ¿Tuvo dolor en alguna parte del cuerpo durante las 4 últimas semanas?

a. No, ninguno
b. Sí, muy poco
c. Sí, un poco
d. Sí, moderado
e. Si, mucho
f. Sí, muchísimo

22) Durante las últimas 4 semanas, ¿hasta qué punto el dolor le ha dificultado su trabajo habitual (incluido el trabajo fuera de casa y las tareas domésticas?

a. Nada
b. Un poco
c. Regular
d. Bastante
e. Mucho

Las siguientes preguntas se refieren a cómo se ha sentido y como le han ido las cosas durante las 4 últimas semanas. En cada pregunta, responda lo que se parezca más a cómo se ha sentido usted.

23) Durante las 4 últimas semanas, ¿Cuánto tiempo se sintió lleno de vitalidad?

a. Siempre
b. Casi siempre
c. Muchas veces
d. Algunas veces
e. Sólo alguna vez
f. Nunca

24) Durante las 4 últimas semanas, ¿Cuánto tiempo estuvo muy nercioso?

a. Siempre
b. Casi siempre
c. Muchas veces
d. Algunas veces
e. Sólo alguna vez
f. Nunca

25) Durante las 4 últimas semanas, ¿Cuánto tiempo se sintió tan bajo de moral que nada podía animarle?

a. Siempre
b. Casi siempre
c. Muchas veces
d. Algunas veces
e. Sólo alguna vez
f. Nunca

26) Durante las 4 últimas semanas, ¿Cuánto tiempo se sintió calmado y tranquilo?

a. Siempre
b. Casi siempre
c. Muchas veces
d. Algunas veces
e. Sólo alguna vez

f. Nunca

27) Durante las 4 últimas semanas, ¿Cuánto tiempo tuvo mucha energía?

a. Siempre
b. Casi siempre
c. Muchas veces
d. Algunas veces
e. Sólo alguna vez
f. Nunca

28) Durante las 4 últimas semanas, ¿Cuánto tiempo se sintió desanimado y triste?

a. Siempre
b. Casi siempre
c. Muchas veces
d. Algunas veces
e. Sólo alguna vez
f. Nunca

29) Durante las 4 últimas semanas, ¿Cuánto tiempo se sintió agotado?

a. Siempre
b. Casi siempre
c. Muchas veces
d. Algunas veces
e. Sólo alguna vez
f. Nunca

30) Durante las 4 últimas semanas, ¿Cuánto tiempo se sintió feliz?

a. Siempre
b. Casi siempre
c. Muchas veces
d. Algunas veces
e. Sólo alguna vez
f. Nunca

31) Durante las 4 últimas semanas, ¿Cuánto tiempo se sintió cansado?

a. Siempre
b. Casi siempre
c. Muchas veces
d. Algunas veces
e. Sólo alguna vez
f. Nunca

32) Durante las 4 últimas semanas, ¿con qué recurrencia la salud física o los problemas emocionales le han dificultado sus actividades sociales (como visitar a amigos o familiares)?

a. Siempre
b. Casi siempre
c. Muchas veces
d. Algunas veces
e. Sólo alguna vez
f. Nunca

Por favor, diga si le parece cierta o falsa cada una de las siguientes frases

33) Creo que me pongo enfermo más fácilmente que otras personas

a. Totalmente cierta
b. Bastante cierta
c. No lo sé
d. Bastante falsa
e. Totalmente falsa

34) Estoy tan sano como cualquiera

a. Totalmente cierta
b. Bastante cierta
c. No lo sé
d. Bastante falsa
e. Totalmente falsa

35) Creo que mi salud va a empeorar

a. Totalmente cierta
b. Bastante cierta
c. No lo sé
d. Bastante falsa
e. Totalmente falsa

36) Mi salud es excelente

a. Totalmente cierta
b. Bastante cierta
c. No lo sé
d. Bastante falsa
e. Totalmente falsa

The scores of each of the 8 dimensions of the SF-36 range between values 0 and 100. 100 being a result that indicates optimal health and 0 would reflect a very bad state of health. Scores above or below 50 indicate better or worse health status,

Tabla1. Contenido de las escalas del SF-36

		Significado de las puntuaciones de 0 a 100	
Dimensión	N.º de ítems	«Peor» puntuación (0)	«Mejor» puntuación (100)
Función física	10	Muy limitado para llevar a cabo todas las actividades físicas, incluido bañarse o ducharse, debido a la salud	Lleva a cabo todo tipo de actividades físicas incluidas las más vigorosas sin ninguna limitación debido a la salud
Rol físico	4	Problemas con el trabajo u otras actividades diarias debido a la salud física	Ningún problema con el trabajo u otras actividades diarias debido a la salud física
Dolor corporal	2	Dolor muy intenso y extremadamente limitante	Ningún dolor ni limitaciones debidas a él
Salud general	5	Evalúa como mala la propia salud y cree posible que empeore	Evalúa la propia salud como excelente
Vitalidad	4	Se siente cansado y exhausto todo el tiempo	Se siente muy dinámico y lleno de energía todo el tiempo
Función social	2	Interferencia extrema y muy frecuente con las actividades sociales normales, debido a problemas físicos o emocionales	Lleva a cabo actividades sociales normales sin ninguna interferencia debido a problemas físicos o emocionales
Rol emocional	3	Problemas con el trabajo y otras actividades diarias debido a problemas emocionales	Ningún problema con el trabajo y otras actividades diarias debido a problemas emocionales
Salud mental	5	Sentimiento de angustia y depresión durante todo el tiempo	Sentimiento de felicidad, tranquilidad y calma durante todo el tiempo
Ítem de Transición de salud	1	Cree que su salud es mucho peor ahora que hace 1 año	Cree que su salud general es mucho mejor ahora que hace 1 año

ANEX 8: HADS

HOSPITAL ANXIETY AND DEPRESSION SCALE
Versión original de Zigmond y Snaith, 1983

Este cuestionario ha sido diseñado para ayudarnos a saber cómo se siente usted. Lea cada frase y marque la respuesta que más se ajusta a cómo se sintió durante la semana pasada. No piense mucho las respuestas. Lo más seguro es que si responde deprisa sus respuestas se ajustarán mucho más a cómo realmente se sintió.

1. Me siento tenso o nervioso.
- ❑ Todos los días
- ❑ Muchas veces
- ❑ A veces
- ❑ Nunca

2. Todavía disfruto con lo que antes me gustaba.
- ❑ Como siempre
- ❑ No lo bastante
- ❑ Sólo un poco
- ❑ Nada

3. Tengo una sensación de miedo, como si algo horrible me fuera a suceder.
- ❑ Definitivamente y es muy fuerte
- ❑ Sí, pero no es muy fuerte
- ❑ Un poco, pero no me preocupa
- ❑ Nada

4. Puedo reírme y ver el lado divertido de las cosas.
- ❑ Al igual que siempre lo hice
- ❑ No tanto ahora
- ❑ Casi nunca
- ❑ Nunca

5. Tengo mi mente llena de preocupaciones.
- ❑ La mayoría de las veces
- ❑ Con bastante frecuencia
- ❑ A veces, aunque no muy a menudo
- ❑ Sólo en ocasiones

6. Me siento alegre.
- ❑ Nunca
- ❑ No muy a menudo
- ❑ A veces
- ❑ Casi siempre

7. Puedo estar sentado confortablemente y sentirme relajado.
- ❑ Siempre
- ❑ Por lo general
- ❑ No muy a menudo
- ❑ Nunca

8. Me siento como si cada día estuviera más lento.
- ❑ Por lo general, en todo momento
- ❑ Muy a menudo
- ❑ A veces
- ❑ Nunca

9. Tengo una sensación extraña, como si tuviera mariposas en el estómago.
- ❑ El Nunca
- ❑ En ciertas ocasiones
- ❑ Con bastante frecuencia
- ❑ Muy a menudo

10. He perdido interés en mi aspecto personal.
- ❑ Totalmente
- ❑ No me preocupeo tanto como debiera
- ❑ Podría tener un poco más de cuidado
- ❑ Me preocupo al igual que siempre

11. Me siento inquieto, como si no pudiera parar de moverme.
- ❑ Mucho
- ❑ Bastante
- ❑ No mucho
- ❑ Nada

12. Me siento optimista respecto al futuro.
- ❑ Igual que siempre
- ❑ Menos de lo que acostumbraba
- ❑ Mucho menos de lo que acostumbraba
- ❑ Nada

13. Me asaltan sentimientos repentinos de pánico.
- ❑ Muy frecuentemente
- ❑ Bastante a menudo
- ❑ No muy a menudo
- ❑ Rara vez

14. Me divierto con un buen libro, la radio, o un programa de televisión.
- ❑ A menudo
- ❑ A veces
- ❑ No muy a menudo
- ❑ Rara vez

HADS - Ansiedad

1. Me siento tenso(a) o nervioso(a)
3. Tengo una sensación de miedo, como si algo horrible me fuera a suceder
5. Tengo mi mente llena de preocupaciones
7. Puedo estar sentado(a) tranquilamente y sentirme relajado(a)
9. Tengo una sensación extraña, como de "aleteo" en el estomago
11. Me siento inquieto(a), como si no pudiera parar de moverme
13. Me asaltan sentimientos repentinos de pánico

HADS –Depresión

2. Todavía disfruto con lo que antes me gustaba
4. Puedo reírme y ver el lado divertido de las cosas
6. Me siento alegre
8. Me siento como si cada vez estuviera más lento
10. He perdido el interés en mi aspecto personal
12. Me siento optimista respecto al futuro
14. Me divierto con un buen libro, la radio o un programa de televisión

Likert scale 0-3

Each subscale 0-21

Scoring:

Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

ANEX 9: DATA COLLECTION NOTEBOOK

Visita

Data:

Codi pacient:

Edat:

Sexe: HOME DONA

-Criteris de selecció:

Criteris d'inclusió	si	no
Pacient >18 años		
Cumpleix criteris artritis reumatoide refractària		
Ha firmat el consentimiento informat		
Criteris d'exclusió		
Cualsevol patologia o circumstancia que contraindiqui la recollida de dades		

Data diagnòstic de la malaltia:

Data inici del tractament:

FR:

ACCP:

Presència erosions radiològiques:

Tratament actual i dosis:

AINEs:

Corticoides:

Fármacos modificadors de la malaltia (FMM):

Malalties concomitants, comorbilitats: Fibromialgia, artrosis, historia prèvia de depressió i ansietat

Manifestacions extraarticulars (pneumònia, síndrome seca):

Tabac:

IMC:

Evaluació clínica

NAD: NAT:

EVA dolor: EVA estat general:

EVA mèdic:

VSG: PCR (mg /L):

ADAs: SI NO

Ecografia articular: SI NO
(presencia de sinovitis)

-Índex activitat

DAS28 VSG

DAS28 PCR

RAPID 3

-Resultats dels qüestionaris:

HADS

SF 36

ANEX 10: Informed Consent

CONSENTIMIENTO INFORMADO POR ESCRITO

RELACIÓN ENTRE LOS TRASTORNOS PSICOSOMÁTICOS (DEPRESIÓN Y ANSIEDAD) Y LA ARTRITIS REUMATOIDE REFRACTARIA

Apreciada Sr/a.:

Usted presenta una Artritis Reumatoide (AR). Es una enfermedad reumática crónica que puede producir daño articular progresivo, se puede asociar a dificultad para realizar las tareas habituales y puede deteriorar la calidad de vida. En los últimos años la enfermedad ha experimentado una notable mejoría del pronóstico gracias a la aplicación de nuevas estrategias terapéuticas eficaces y la introducción del tratamiento precoz, pero aun así hay pacientes que siguen teniendo dificultades para controlar la enfermedad.

El objetivo del estudio es ver si existe alguna relación entre trastornos psicosomáticos como la ansiedad y la depresión y la artritis reumatoide difícil de tratar.

Beneficios asociados al estudio. A corto-medio plazo, de este estudio se obtendrá información muy útil que nos ayudará a mejorar el manejo de los pacientes con artritis reumatoide refractaria. La hipótesis de estudio es que los pacientes falsos refractarios tienen una prevalencia más elevada de depresión y ansiedad que los verdaderos refractarios.

Usted puede negarse a participar en el estudio y esto no será ningún inconveniente para el control de su enfermedad ni afectará en absoluto en el tratamiento que se le realizará ni al seguimiento posterior.

La participación en el estudio no supone la realización de pruebas extraordinarias. Usted no obtendrá ningún beneficio ni inconveniente. Se le realizarán los procedimientos habituales de valoración clínicos y analíticos de la enfermedad y evaluación de la respuesta al tratamiento y se le pasará un cuestionario para valorar su estado de salud. Las muestras de sangre se destruirán después de la determinación de los parámetros bioquímicos que queremos estudiar.

En el caso de que acepte participar, le garantizamos el tratamiento confidencial de sus datos personales (se cumplirá los requisitos de la *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales*) y de los resultados que resulten de los estudios. En este estudio sólo se le identificará mediante sus iniciales y un número de registro.

Para realizar este estudio se requiere una donación de sangre por parte del paciente, pero de ningún modo se le realizará una maniobra añadida a las estrictamente necesarias para el diagnóstico y seguimiento de su enfermedad de base. De este modo no supondrá ninguna molestia añadida para el paciente. Las muestras se almacenarán en el Hospital de Santa Caterina y Josep Trueta respetando estrictamente las

condiciones de confidencialidad de los datos y se asignará a cada muestra un único código que la identificará a partir de ese momento.

Usted tiene derecho a conocer los resultados del estudio si lo desea. Si quiere ser informado de los resultados del estudio, anote un teléfono en el que podamos localizarle y le informaremos en cuanto dispongamos de ellos.

Teléfono: ……

Se le entregará una copia del consentimiento firmado.

Yo, _____ (nombre y apellidos del participante):

He leído la hoja de información que se me ha entregado.

He podido hacer preguntas sobre el estudio.

He recibido suficiente información sobre el estudio.

He hablado con _____ (nombre y apellidos del investigador).

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

- Cuando quiera

- Sin tener que dar explicaciones.

- Sin que esto repercuta en mis cuidados médicos

Estoy informado de:

- la existencia de fichero automatizado automático de datos de carácter personal que serán almacenadas en un fichero destinado al tratamiento informático de la información obtenida

- la información podrá ser utilizada exclusivamente para finalidades científicas

- el fichero estará en manos del investigador principal y tengo derecho al acceso, rectificación, cancelación y oposición dirigiéndome por escrito al titular.

Acepto libremente participar en este estudio.

Firma del participante Fecha (a completar por el participante)

Firma del investigador Fecha (a completar por el investigador)

(persona que obtiene el consentimiento)

CONSENTIMENT INFORMAT PER ESCRIT

RELACIÓ ENTRE ELS TRASTORNS PSICOSOMÀTICS (DEPRESSIÓ I ANSIETAT) I L'ARTRITIS REUMATOIDE REFRACTÀRIA

Apreciat Sr / a.:

Vostè presenta una Artritis Reumatoide (AR). És una malaltia reumàtica crònica que pot produir dany articular progressiu, es pot associar a dificultat per a realitzar les tasques habituals i pot deteriorar la qualitat de vida. En els últims anys la malaltia ha experimentat una notable millora del pronòstic gràcies a l'aplicació de noves estratègies terapèutiques eficaces i la introducció del tractament precoç.

L'objectiu de l'estudi és veure si hi ha alguna relació entre trastorns psicosomàtics com l'ansietat i la depressió i l'artritis reumatoide difícil de tractar.

Beneficis associats a l'estudi: curt-mig termini, d'aquest estudi s'obtindrà informació molt útil que ens ajudarà a millorar el maneig dels pacients amb Artritis Reumatoide. La hipòtesi d'estudi és que que els pacients falsos refractaris tenen una prevalença més elevada de depressió i ansietat que els veritables refractaris.

Vostè pot negar-se a participar en l'estudi i això no suposarà cap inconvenient pel control de la seva malaltia i no afectarà en absolut en el tractament que se li realitzarà ni el seguiment posterior.

La participació en l'estudi no suposa la realització de proves extraordinàries. Vostè no obtindrà cap benefici ni inconvenient. Se li realitzaran els procediments habituals de valoració clínics i analítics de la malaltia i l'avaluació de la resposta al tractament i se li passarà un qüestionari per a valorar el seu estat de salut. Les mostres de sang es destruiran després de la determinació dels paràmetres bioquímics que volem estudiar.

En el cas que accepti participar, li garantim el tractament confidencial de les seves dades personals (es complirà els requisits de la Llei Orgànica 3/2018, de 5 de desembre, de Protecció de Dades Personals i garantia dels drets digitals) i dels resultats que resultin dels estudis. En aquest estudi només se l'identificarà mitjançant les seves inicials i un número de registre.

La participació en l'estudi no suposa la realització de proves extraordinàries; se li realitzaran els procediments habituals de valoració clínics i analítics de la malaltia, l´avaluació de la resposta al tractament i se li passarà un qüestionari per a valorar el seu estat de salut. Les mostres de sang es destruiran després de la determinació dels paràmetres bioquímics que volem estudiar.

Vostè té dret a conèixer els resultats de l'estudi si ho desitja. Si vol ser informat dels resultats de l'estudi, anoti un telèfon en el qual puguem localitzar i l'informarem quant disposem d'ells.

Telèfon: ……

Se li farà entregar d'una còpia del consentiment firmat.

Jo, _____ (nom i cognoms del participant).

He llegit el full d'informació que se m'ha lliurat.

He pogut fer preguntes sobre l'estudi.

He rebut suficient informació sobre l'estudi.

He parlat amb _____ (nom i cognoms de l'investigador).

Comprenc que la meva participació és voluntària.

Comprenc que puc retirar-me de l'estudi:

- Quan vulgui

- Sense haver de donar explicacions.

- Sense que això repercuteixi en les meves cures mèdiques

Estic informat de:

- l'existència de fitxer automatitzat automàtic de dades de caràcter personal que seran emmagatzemades en un fitxer destinat al tractament informàtic de la informació obtinguda

- la informació podrà ser utilitzada exclusivament per a finalitats científiques

- el fitxer estarà en mans de l'investigador principal i tinc dret a l'accés, rectificació, cancel·lació i oposició dirigint-me per escrit al titular.

Estic d'acord a participar lliurement en aquest estudi.

Firma del participant Data (a completar pel participant)

Firma de l'investigador Data (a completar per l'investigador)

(persona que obté el consentiment)