Universitat de Girona
Facultat de Medicina

Tofacitinib versus a second anti-TNF drug after first anti-TNF failure to treat active Rheumatoid Arthritis

FINAL DEGREE PROJECT

RHEUMATOLOGY DEPARTMENT

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Dedique aquest treball a la meua família que des de la distancia sempre han sigut el suport més fort.

Papa, sé que estaries orgullós de mi.

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ABSTRACT

Background: Rheumatoid arthritis is chronic inflammatory disease which could produce destruction of the joints, deformity in the joint zones and disability in the patient's daily life.

So it's important to treat correctly these patients. Biological therapy has greatly improved the treatment of RA, since the appearance of anti-TNF they have been the most used. Unfortunately, one-third of patients with rheumatoid arthritis show inadequate response to TNF inhibitors.

Nowadays, there isn't guidance on choosing the next treatment in these cases. The scientific literature supports both steps, the switching, to choose a second anti-TNF drug; or change to therapeutic target.

Tofacitinib is an oral Janus kinase inhibitor, a new therapeutic target, for the treatment of active rheumatoid arthritis.

Objectives: The objective of our study is to compare the efficacy of tofacitinib versus a second anti-TNF after a first failure of anti-TNF in the treatment of patients with active rheumatoid arthritis.

Design: Multicentric, open and randomized controlled clinical trial with parallel groups.

Methods: A total of 376 patients enrolled in this study will be randomized in two groups (group A and group B). The group A, with 188 patients, will receive two oral pills of tofacitinib (5mg and 5mg); and the second group, group B with 188 patients will receive an injections of anti-TNF drug.

The efficacy of the treatment (primary outcome) will be the proportion of patients with a good or moderate DAS28 response on the EULAR scale in the 6th month of treatment. Secondary outcomes will also be seen in month 3 and 12, as well as SDAI, CDAI, HAQ and possible adverse effects.

Participants: Patients with active rheumatoid arthritis with insufficient response to first anti-TNF drug, reflected in DAS28-ESR with >3.2, with stable dose of methotrexate within 4 weeks of enrollment.

Key words: rheumatoid arthritis, anti-JAK, anti-TNF, DAS28, SDAI, CDAI, HAQ

ABREVIATIONS

ACPA	Anti-citrullinated protein antibodies
ACR	American College Rheumatology
APR	Acute-phase reactants
CDAI	Clinical Disease Activity Index
CRP	C - reactive protein
csDMARD	conventional synthetic Disease Modifying Antirheumatic Drug
DAS	Disease activity score
DMARD	Disease modifying antirheumatic drugs
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HAQ	Health assessment questionnaire
IL	Interleukine
JAK	Janus kinase inhibitors
JIA	Juvenile Idiopathic arthritis
MCP	Metacarpophalangeal
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
PIP	Proximal interphalangeal
RA	Rheumatoid Arthritis
RF	Rhematoid Factor
SDAI	Simplified Disease Activity Index
TNF	Tumor Necrosis Factor

1. INTRODUCTION

1.1. RHEUMATOID ARTHRITIS

1.1.1. Definition

Rheumatoid arthritis is a serious chronic systemic autoimmune disease of unknown etiology that mainly affects the synovial joints but also can affect systemically (1). It's characterized by symmetric articular inflammation. Persistent synovial inflammation destroys the articular cartilage, causes erosions in the bone epiphyses and in advanced phases deforms the joints and causes functional impotence. In some serious cases life expectancy may decrease. But its evolution and its clinic are variable. (2)

1.1.2. Epidemiology

RA affects 0.5% of adults in our country; it's more frequent in women, proportion 3:1. It could appear at any age but frequently it appears between 40-60 years old. (3)

The incidence rate increases in relatives (2 to 3 times) and in monozygotic twins have a concordance about 20-30%; it shows a genetic component. Also, in smokers the risk is 1,5-2 higher. (4)

1.1.3. Etiology and pathogenesis

Although the pathogenesis of rheumatoid arthritis remains incompletely understood, much insight into the cellular and molecular mechanisms involved. It has been observed that there is a genetic basis that constitutes 60% of the risk of suffering from the disease, and one or different environmental antigens would act on it, causing an inflammatory reaction perpetuated by autoinflammatory mechanisms.(2)

Infectious agents could be the causative agents of the disease. Viruses such as Epstein-Barr virus and other herpes viruses, parvovirus B19, retroviruses; bacteria such as Porphyromonas gingivalis and mycobacteria. But there is no evidence that causally implicates a specific infectious agent to develop RA in a predisposed subject(5). Smoking has also been linked to the development of arthritis. (6)

The genetic basis is based on the familial aggregation of the disease, on the 4 times greater agreement between monozygotic twins than on dizygotic twins and as genetic factors include

genes involved in the immune response such as HLA-DRB1 (DR4 and DR1); both share the amino acid sequence glutamine-leucine-arginine-alanine-alanine (QKRAA), called shared epitope. (7)

More than 30 genes are known associated with the susceptibility and / or severity of the disease, which are related to response or activation of T lymphocytes or elements that regulate cellular responses to inflammation.(8)

IMMUNOPATHOLOGY OF RA

The inflammatory infiltrate of the synovial membrane consists of T lymphocytes (CD4+ > CD8+), B lymphocytes, which differentiate locally in plasma cells that produce antibodies (rheumatoid factor) that recognize the constant fraction (cF) of the IgG antigen, and citrullinated anti-peptide antibodies (anti-CCP) (6) , which end up forming immunocomplexes. In the rheumatoid synovial membrane there are activated cells such as fibroblasts, mast cells and mesenchymal stromal cells.(9)

The cytokines secreted by macrophages and T lymphocytes are intercellular mediators, especially the tumor necrosis factor alpha (TNF-α) and the interleukins 1 and 6 (IL-1, IL-6) that are involved in the inflammatory response. They induce the activation of intracellular cascades of activation of proinflammatory genes such as collagenases and proteases, proteolytic enzymes that degrade the cartilage matrix and induce the differentiation of osteoclasts to destroy adjacent bone and cartilage, causing the erosions. Prostaglandins, formation of free radicals, release of liposomal enzymes, phagocytosis and complement activation as additional mechanisms to the chronic inflammatory response. (7)

So it can be considered an autoimmune disease; in which, starting from an initial non-specific inflammatory stimulus, the process is amplified by the activation of T cells that leads to a phase of chronic inflammation with joint injuries.

1.1.4. Pathologic anatomy

Rheumatoid synovitis is characterized by a cellular infiltrate and a hyperplasic growth of the synovial membrane. The cellular infiltrate is composed mainly of macrophages and T and B lymphocytes, and in lesser amounts mast cells or dendritic cells. They are organized diffusely or forming perivascular aggregates, and contain vessels called high endothelial venules, dendritic and follicular cells.

As for the growth and hyperplasia of fibroblastic synoviocytes, they form multiple superimposed layers, interspersed with macrophages that at their ends form *pannus*, which invades the adjacent bone and cartilage. At the edge there are mature and active osteoclasts. The synovocytes produce the destruction of the cartilage by synthesis of enzymes that degrade the cartilaginous matrix. In addition, neovessels are developed that nourish, help the growth of synovial tissue and allow the adhesion of cells that form the synovial infiltrate; but the consumption of oxygen exceeds the contribution leading to a chronic hypoxia perpetuating a proangiogenic and proinflammatory state. All this causes the persistence of chronic synovitis. (10) [Figure 1]

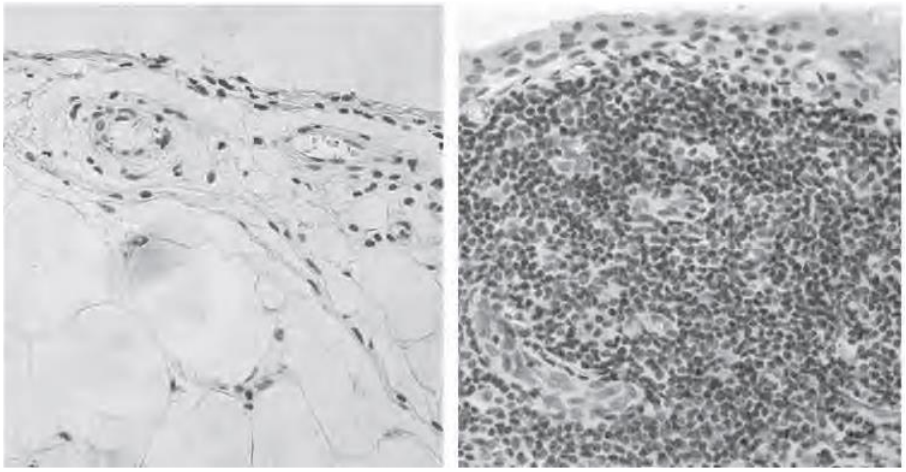

Figure 1. Histopathology of normal synovial (left) and rheumatoid (right). From 'Manual SER'

1.1.5. Clinical features and complications

The clinical features are important point to diagnose RA. Its symptomatology includes inflammatory pain that gets worse at rest, joint inflammation with increased joint volume due to synovial fluid effusion, joint stiffness that is difficulty to move joints after a time of rest and it's caused by accumulation of inflammatory fluid in muscles and joints, atrophy and muscular weakness and in advanced cases, joint deformity.

Initial phase

Joint manifestations such as bilateral and symmetrical arthritis in hands that progress slowly and progressively predominate. And it's characterized by a morning stiffness of more than an hour. (1)

State phase

Pain synovitis occurs with pressure; swelling, local heat and a decrease in joint mobility, so muscle atrophy may appear. (1)

Advanced phase

Joint deformities can appear:

- Ulnar deviation of the fingers
- Fingers in gooseneck
- Thumb in Z
- Atlantoaxial dislocation
- Rheumatoid nodules: appear in 20-30% of cases. They are subcutaneous nodules located in areas of friction or pressure. (1) [Figure 2]

Figure 2. . Rheumatoid nodule in elbow. From 'Manuel SER', author: Cr. A. Naranjo

Joint manifestations: could be affected hands and wrists, the metacarpophalangeal and proximal interphalangeal joints are the joints that are most affected; shoulders, elbows, feet, knees, hip and backbone.

Extraarticular manifestation:

1. Lung: pleurisy, nodules, interstitial lung disease
2. Skin: Rheumatoid nodules, skin ulcers
3. Heart: pericarditis, cardiovascular disease
4. Nervous system: carpal tunnel syndrome

5. Hematopoietic organs: Felty's syndrome (RA+ neutropenia+ splenomegaly)
6. Eyes: Sjögren's syndrome, cataract
7. Kidney
8. Gastrointestinal tract
9. Rheumatoid vasculitis
10. Musucular atrophy
11. Osteoporosis
12. Cancer: lymphoma, lung cancer, skin cancer
13. Infection: septic arthritis, tuberculosis
14. Amyloidosis

1.1.6. Activity rates and response to treatment

To evaluate the evolution of the disease there are different indexes:

- **DAS28:** is a tool for assessing disease activity and response to treatment. The result of DAS is calculated by using a calculator that includes:
  - Number of swollen joints
  - Number of painful joints
  - ESR
  - Evaluation of disease activity according to the patient using the visual analogue scale (VAS, 0-100).

  The range of possible values is 0-9.4. DAS can evaluate the activity of the disease [Table 1] and the response to treatment [Table 2].

Remission	Low activity	Moderate activity	High activity
<2,6 points	≤3,2	>3,2 and ≤5,1	>5,1

Table 1. Evaluation of activity of the disease.

Good response	Moderate response	Without response
↓ ≥1,2 of activity + low activity	↓ >0,6 - <1,2 + low or moderate activity; or ↓ ≥ 1,2 + high activity	↓>0,6 - <1,2 + high activity

Table 2. Evaluation of response of the treatment. ↓: decrease

- **SDAI** Simplified Disease Activity Index)(11) [Annex 1]

Number of painful joint + number of swollen joints + VAS (Visual Analogue Scale) evaluated by the patient + VAS evaluated by the physician + PCR (0,1-10mg/dl)

The range of possible values is 0,1-86.

- Activity of disease: Remission (≤3,3); low activity (≤11), moderate activity (>11,≤26); high activity (>26).
- Response of treatment: good response (decrease >21), moderate response (decrease 10-21), without response (≤9).

- **CDAI** (Clinical Disease Activity Index)(12) [Annex 2]

Number of painful joints + number of swollen joints + VAS evaluated by the patient + VAS evaluated by the physician

The range of possible values is 0,1-76.

- Activity of disease: Remission (≤2,8), low activity (≤10), moderate activity (>10, ≤22), high activity (>22).

- **HAQ** (Health Assessment Questionnaire)(13) [Annex 3]: is a functional assessment questionnaire with 20 items that assess self-perceived physical disability in order to carry out various basic activities of daily life grouped into eight areas. It's For the calculation, the highest score is taken as representative of each of the 8 subgroups, all points are summed and divided by 8. This index varies from 0 to 3.

  The value of the HAQ-DI index can be interpreted in terms of three categories:

  - From 0 to 1: mild difficulties to moderate disability,
  - From 1 to 2: disability moderate to severe,
  - From 2 to 3: severe to very severe disability.

- **Boolean index**

  The remission is considered if the result of the following sections is ≤1:

  - 28 tender joints ≤1

- 28 swollen joints ≤1
- CRP ≤1mg/dl
- Visual analogue scale ≤1 cm

- **ACR Criteria (20%, 50%, 70%)** (14)
  - Improvement ≥20, 50, 70% in the count of painful joints
  - Improvement ≥ 20, 50, 70% in the count of inflamed joints
  - Improvement ≥20, 50, 70% in the three of the following:
    1. Evaluation of pain by patient
    2. Overall assessment by patient
    3. Overall assessment by doctor
    4. Self-assessment of disability by patient
    5. Acute phase reactors

1.1.7. Diagnosis

The diagnosis of RA is based on the clinical presentation of the patient. Laboratory tests, radiological images and ACR or EULAR criteria confirm the diagnosis.

- *Laboratory tests*:
  - **RF**: is an antibody against cF fraction of IgG. It isn't specific of RA but if it's positive indicates disease persistence (PPV 85%) and radiological progresion.
  - **ACPA**: is the major predictor of the clinical course of RA. With sensitivity of 41-66% but una specificity of 91-100%. Both its presence and the value of its title are important as it is related to gravity and radiographic progression.
  - **Acute-phase reactants**: **ESR** and **CRP** are related to disease activity, radiological progression, and response to therapy.
  - **Genetic markers**
- *Imaging tests*: observing erosions by **radiography** has a high specificity to discriminate persistent arthritis and is a predictor factor of progression. (15)

  Ultrasound and MRI are more sensitive to the detection of synovitis and erosions but are often used when the clinic is questionable.

1.1.8. Criteria

✓ **American Rheumatism Association 1987 criteria for the classification of Rheumatoid Arthritis.** The criteria are used as clinical guidelines for diagnosing RA. But these criteria do not include findings of synovial fluid (SF) analysis and require no exclusion criteria. (16) [Table 3]

Table 3: 1987 Rheumatoid Arthritis classification of ACR (17)

1. **Morning stiffness***	Morning stiffness in and around the joints, at least 1 hour of duration.
2. **Arthritis of ≥ 3 joint areas***	At least 3 joint areas simultaneously have had soft tissue swelling or fluid observed by a physician. The 14 areas are right or left PIP, MCP, wrist, elbow, knee, ankle and MTP joints.
3. **Arthritis of hand joints***	At least 1 area swollen: wrist, MCP or PIP joint.
4. **Symmetric arthritis***	Simultaneous involvement of the same joint area on both sides of the body.
5. **Rheumatoid nodules**	Subcutaneous nodules, over bony prominences or extensor surfaces or in juxtaarticular regions, observed by a physician.
6. **Serum rheumatoid factor**	Demonstration of abnormal increase of serum rheumatoid factor.
7. **Radiographic changes**	Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or bony decalcification localized in the involved joints.
	A score of **≥4/7** is needed to diagnose a RA.

* Criteria 1 to 4 must be present for at least 6 weeks

✓ **Criterios de ACR/EULAR 2010 para la clasificación de RA**

This classification system focuses on features at earlier stages of disease that are associated with persistent and/or erosive disease. Also, it's detected who patients benefit from early treatment to prevent or minimize the occurrence of the undesirable consequences of the RA. (18) [Table 4]

Target population is who:

- Has at least 1 joint with definite clinical synovitis (swelling).
- With synovitis not better explained by another disease.

Table 4. The 2010 American College of Rheumatology/European League against Rheumatism classification criteria for RA. (18)

Joint involvement	Serology	Acute-phase reactants	Duration of symptoms
1 large joint: *0 points* 2-10 large joints: *1 point* 1-3 small joints: *2 points* 4-10 small joints: *3 points* >10 joints (at least 1 small joint): *5 points*	Negative RF and ACPA: *0 points* Low-positive RF or ACPA *2 points* High-positive RF or ACPA *3 points*	Normal CRP and ESR *0 points* Abnormal CRP or normal ESR: *1 point*	<6 weeks: *0 points* ≥6 weeks: *1 point*
A score of **≥ 6/10** is needed for classification of a patient as having definite RA			

1.1.9. Differential diagnosis

Regarding the differential diagnosis, in the old people, arthrosis of hands, polymyalgia rheumatica and calcium pyrophosphate crystal deposition disease are the most common differential diagnoses.

In the most young people would be reactive arthritis, arthritis by virus (parvovirus B19) and other inflammatory rheumatic diseases such as ankylosing spondylitis, psoriatic arthritis, and the collagenosis (lupus erythematosus, scleroderma, polymyositis). Other less frequent entities that may raise differential diagnosis are multicentric reticulohistiocytosis, hemochromatosis and sarcoidosis.

1.1.10. Treatment

Reduction of synovial inflammation is the main goal of treatment and all strategies that achieve reduction of synovitis are associated with improvement of pain, structural damage and functional ability.(19)

Remission is the ideal therapeutic goal, and is easiest to achieve in new-onset RA. In advanced disease, low activity may be an acceptable goal.

The therapeutic objective must be attained, at least partially, at 3 months and, at the most, at 6 months. If there is no response at 3 months, it should be replaced, as the activity at 3 and 6 months makes it possible to predict the response in the medium and long term.(20)

The use of indexes (**DAS28-ESR**, **SDAI**, **CDAI**, and **HAQ**) is the most appropriate way to assess global inflammatory activity and response to treatment in clinical practice.

Treatment of RA includes disease-modifying drugs (DMARDs), which may be synthetic or biological, as well as anti-inflammatories, analgesics, corticosteroids, and non-pharmacological physical measures, but DMARDs should be started as soon as the disease is diagnosed to take advantage of a possible therapeutic window of opportunity(21). **Methotrexate** is commonly used (22,23). When it is not effective or the patient does not tolerate it, others such as **leflunomide** (24), **sulfasalazine** or **hydroxychloroquine** can be used in monotherapy or in association and if there is no response, a biologic is associated. DMARDs improve inflammatory activity, pain and functional ability, delay structural radiographic damage and prevent long-term disability.

When the treatment goal isn't achieved by methotrexate therapy, biologic agents should be introduced early in the course of treatment. (25)The biologics most frequently used in the first line are anti-TNF (**infliximab, etanercept, adalimumab, golimumab, certolizumab**) (26), but drugs can also be used that target other targets: co-stimulating anti-molecules (**abatacept**), IL-6 receptor (**tocilizumab, sarilumab**), anti-CD20 (**rituximab**) or anti-IL-1 (**anakinra**). In general, biological drugs are used in association with methotrexate because their efficacy is greater and because in many cases their risk of loss of secondary response due to immunogenicity and development of neutralizing antipharmaceutical antibodies is reduced.

Unfortunately, one third part of patients will discontinue therapy with their first TNF inhibitor for various reasons(25):

- *Primary non-response*: is defined as lack of improvement in clinical signs or symptoms after initiating induction therapy; it's about 30-40% (27). So we must change to a drug of a different class rather

switch to an alternative TNF inhibitor. Factors that seem increase the risk of primary non-response include males with higher body mass index, smoking high IL-8 level, high TNF.(28)

- *Secondary non-response*: also known as loss of response, describes those cases where the patient had an initial improvement but later develop a relapse of disease; it's about 30-40% patients(27). So we must switch to another TNF inhibitor or change to a drug of a different class.

  The presence of antidrug antibodies is associated with loss of response and possible infusions reactions; in these cases, therapy should be changed to another anti-TNF or a biologic of a different class with or without an immunomodulator to prevent future immunogenicity.(29)
- *Toxicity*: either switch to another TNF inhibitor or change to a drug of a different class, but the risk of the same toxic effect needs to be considered.

We now also have synthetic target-oriented DMARD such as **baricitinib** and **tofacitinib** (30), they are inhibitors of Janus kinases, which are molecules involved in the inflammatory cascade (31). Tofacinitib interferes with interleukin-6 signaling and IL-6 is the major activator of acute-phase reactants; so tofacitinib reduces CRP concentrations(32). Tofacitinib, as monotherapy or combined with non-biological DMARDs, mainly methotrexate (33); is indicated in adult patients with active moderate-severe rheumatoid arthritis who have had an inadequate response or intolerance to one or more csDMARD.(34)

The best strategy for treating patients who have experienced a failure to respond to anti-TNF drug is still unknown, so it isn't possible to produce clear guidelines. But treatment should always be tailored to the needs of the individual patient.

In some studies have demonstrated a clinical improvement in the patients, with a failure to the first anti-TNF drug, who changed the therapeutic target, different from the anti-TNF therapeutic target. (26,27,28)

So, tofacitinib could provide an effective treatment option in patients with an inadequate response to TNFi.

Monitoring should be frequent in active disease to observe the progression of the disease (every 1-3 months); if there is no improvement no later than 3 months after starting treatment, or if the goal has not been reached by 6 months, therapy should be adjusted.(21)(38)

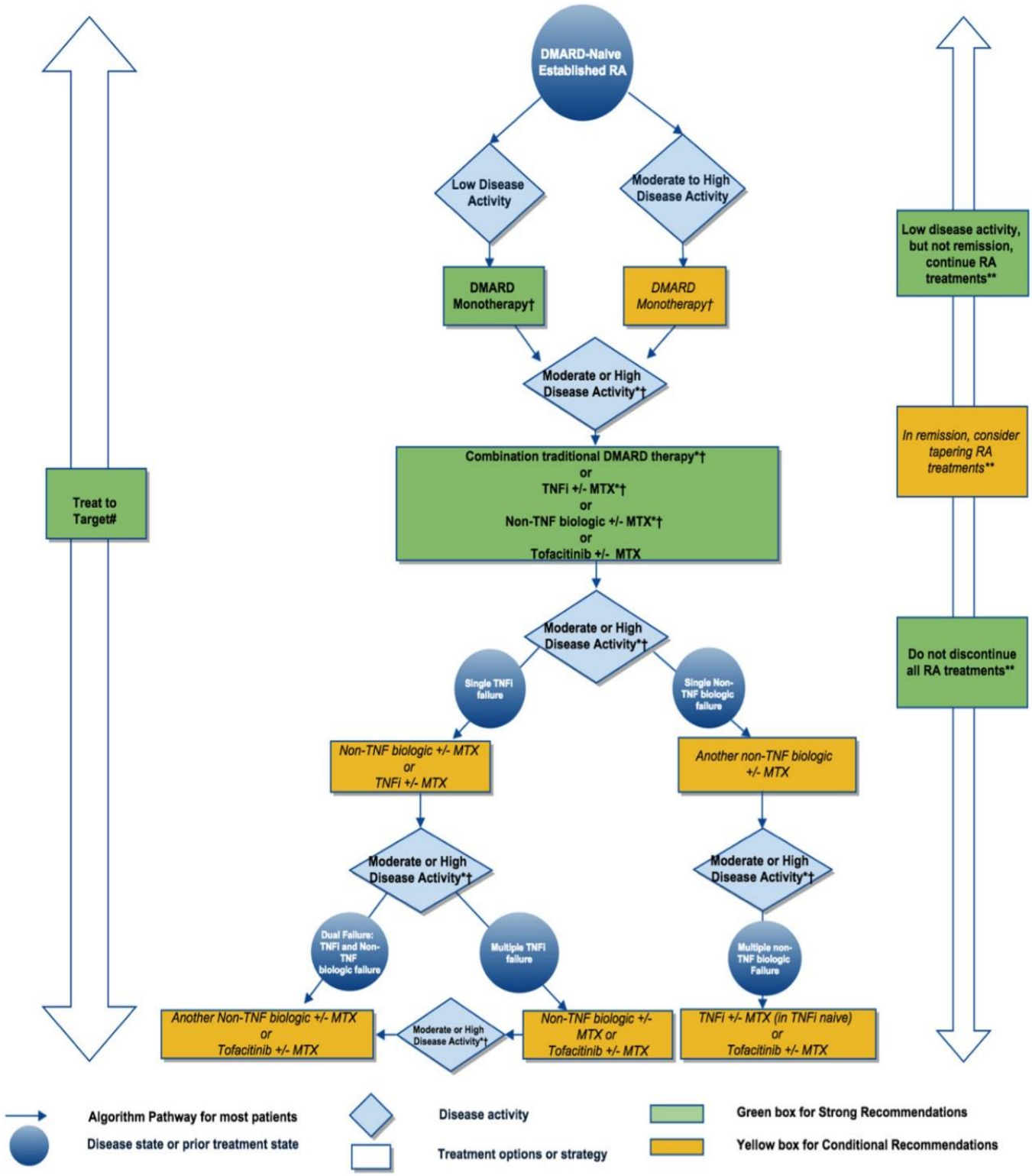

Figure 3. Therapeutic algorithm. From '*2015 reccomendations of EULAR'*

1.1.11. Prognosis

Unfavorable prognostic factors (19, 20):

- Involvement of multiple joints at the onset of the disease
- Early involvement of large joints
- Elevation of VSG and PAR
- Presence of RF and antiCCP
- Presence of erosion and early radiological changes
- Poor functional class (estimated in HAQ)
- Delay in starting treatment
- Extra-articular manifestations
- Presence of genetic markers HLA-DR4/DR1
- Tobacco

It is estimated that 60-90% of patients with undifferentiated arthritis present a progressive course that is associated with joint destruction (41). And they can benefit with early antirheumatic treatment.(42)

1.2. ANTI-TNF DRUGS

1.2.1. INFLIXIMAB (43)

It is a chimeric murine-human IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology.

- **Mechanism of action**

Infliximab is a murino-human chimeric monoclonal antibody that binds with high affinity to both the soluble and transmembrane forms of TNFα.

- **Therapeutic indications**

1. AR: in combination with MTX, it is indicated in patients with active disease when they have not had an adequate response to DMARDs. Or in those adult patients with severe, active and progressive disease not previously treated.

For the treatment of RA, 3 mg/kg administered in intravenous infusion is recommended followed by additional doses of 3 mg/kg in perfusion, at 2 and 6 weeks after the first and then one every 8 weeks.

2. Crohn's disease.
3. Ulcerative colitis
4. Ankylosing spondylitis
5. Arthritis psoriasis
6. Psoriasis

- **Contraindications**
  - Hypersensitivity to the active substance, or to other murine proteins or to excipients (Saccharose Polysorbate 80 Monobasic sodium phosphate)
  - Patients with tuberculosis or other serious infections (septicemia, abscesses and opportunistic infections).
  - Patients with moderate or severe heart failure (class III/IV according to NYHA classification).

1.2.2. ETANERCEPT (44)

Etanercept is a human protein composed of the tumor necrosis factor receptor p75 and the Fc portion of human IgG1, obtained by recombinant DNA technology. Injectable solution.

- **Mechanism of action**

Competitive inhibition of the binding of TNF to the TNFR of the cell surface by preventing the cell response mediated by TNF causing TNF to be biologically inactive.

- **Therapeutic indications**

1. RA: in combination with MTX, is indicated in moderate to severe active RA in adults when DMARDs has been inadequate. It is also indicated in progressive AR that has not been previously treated.

For the treatment of RA the recommended dose is 25 mg of etanercept given twice a week.

2. JIA

3. Arthritis psoriasis

4. Ankylosing spondylitis

5. Axial Spondyloarthritis

6. Plaque psoriasis

- **Contraindications**
  - Hypersensitivity to the active ingredient or to any of the excipients (anhydrous citric acid, sodium citrate dihydrate, sodium chloride, sucrose, L-lysine hydrochloride, sodium hydroxide, hydrochloric acid and water for injectable preparations).
  - Sepsis or risk of sepsis
  - Active, chronic, or localized infections.

1.2.3. ADALIMUMAB (45)

It's a recombinant human monoclonal antibody. Injectable solution.

- **Mechanism of action**

Adalimumab specifically binds to TNF (Tumor Necrosis Factor) and neutralizes its biological function by blocking its interaction with p55 and p75 TNF receptors on the cell surface. Adalimumab also modulates the biological response induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.

- **Therapeutic indications**

1. RA: in moderate to severe active RA that has had an insufficient response to DAMRDs; and those active, severe, and progressive RA that have not received treatment are also treated.

For the treatment of RA the recommended dose is 40 mg adalimumab given every other week as a single dose in subcutaneous injection; although it should be given with MTX, it can be given as monotherapy.

2. Juvenile idiopathic arthritis

3. Arthritis associated with entesitis
4. Ankylosing spondylitis
5. Arthritis psoriasis
6. Hidradenitis suppurativa
7. Plaque psoriasis
8. Crohn's disease
9. Ulcerative colitis
10. Uveitis

- **Contraindications**
    - Hypersensitivity to the active principle of an excipient (Mannitol Polysorbate 80 Water for injectable preparations)
    - Active tuberculosis or other serious infections (sepsis or opportunistic infections)
    - Moderate to severe heart failure (NYHA class III/IV)

1.2.4. CERTOLIZUMAB (46)

It is a Fab' fragment of a recombinant humanized antibody against tumor necrosis factor α (TNFα) expressed in Escherichia coli and conjugated with polyethylene glycol (PEG). Injectable solution.

- **Mechanism of action**

It has a high affinity for the human TNFα which he joins with a dissociation constant (KD) of 90 pM. TNFα is a key pro-inflammatory cytokine that plays a fundamental role in inflammatory processes.

- **Therapeutic indications**

1. RA: in moderate to severe active RA with an insufficient response to DMARDs; or in those severe, active and progressive RA without treatment. For the treatment of RA it is necessary to administer a load dose of 400mg in weeks 0, 2 and 4; and a maintenance dose of 200mg every 2 weeks.
2. Ankylosing spondylitis
3. Axial spondyloarthritis without radiographic evidence
4. Arthritis psoriasis
5. Plaque psoriasis

- **Contraindications**
  - Hypersensitivity to the active ingredient or some excipient (Sodium acetate Sodium chloride Water for injectable preparations)
  - Active tuberculosis or severe infections (sepsis or opportunistic infections)
  - Moderate to severe heart failure (class II/IV according to NYHA).

1.2.5. GOLIMUMAB(47)

Human IgG1κ monoclonal antibody produced in a murine hybridoma cell line using recombinant DNA technology. Injectable solution.

- **Mechanism of action**

Golimumab is a human monoclonal antibody that forms stable complexes of great affinity with the two bioactive forms of human TNF-α, the soluble and the transmembranous, thus preventing the binding of TNF-α to its receptors.

- **Therapeutic Indications**

1. RA: moderate to severe with inadequate response to DMARDs or untreated active, severe and progressive ar.
   For the treatment of RA should be administered, along with MTX, 50mg once a month.
2. JIA
3. Arthritis psoriasis
4. Ankylosing spondylitis
5. Ankylosing Spondyloarthritis
6. Ulcerative colitis

- **Contraindications**
  - Hypersensitivity to the active substance or some excipient (sorbitol)
  - Active tuberculosis or severe infections (sepsis or opportunistic infections)
  - Moderate or severe heart failure (class III/IV at NYHA)

1.2.6. ADVERSE EFFECTS OF ANTI-TNF DRUGS

- *Very frequent* (>1/10): reactions at the injection site, headache, abdominal pain, nausea and vomiting, rash, respiratory tract infections, sinusitis.

- *Frequent* (<1/10): allergic reactions, fever, increases in transaminases, , neutropenia, plaquetopenia ,depression, insomnia, tachycardia, palpitations, psoriasis, , migraine, asthma, dyspnea, dyspepsia.

- Infrequent (<1/100): severe allergic reactions, hepatitis, convulsions, pancreatitis, fainting, tuberculosis, pyelonephritis, vasculitis, opportunistic, neurological or eye infections, melanoma, pleural effusion, facial edema, fatty liver, les, impotence, thyroid alteration.

- *Rare* (>1/1000): bone marrow failure, leukopenia, melanoma, taste alteration, urinary tract disorders, stroke, arteriosclerosis, Raynaud's phenomenon, splenomegalis, anaphylactic shock, multiform erythemaa, Stevens-Johnson syndrome, cardiac arrest, sarcoidosis.

- *Very rare* (<1/1000) medullar aplasia, Guillain-Barre, toxic epidermal necrolysis.

1.3. TOFACITINIB (48)

Tofacitinib is a janus kinase inhibitor. It is recommended at 5 mg/twice daily, administered orally. It is a tablet containing lactose as an excipient.

- **Mechanism of action**

  It is a janus kinase inhibitor that mainly inhibits JAK1 and JAK3, and to a lesser extent JAK2. This causes a transduction blockade of IL-2, IL-6, IL-7, IL-12 interleukins, which results in modulation of the immune and inflammatory response**.**

- **Therapeutic Indications**

  Tofacitinib and MTX are indicated for the treatment of moderate to severe active RA in adult patients who have not responded adequately or are intolerant to one or more disease-modifying anti-rheumatic drugs. Tofacitinib may also be given as monotherapy.

  Dosage should be adjusted, usually to 5mg/day in cases:

  - Patients taking CYP3A4 inhibitors (ketoconazole) or CYP2C19 inhibitors (fluconazole).
  - Severe renal failure (creatinine clearance <30ml/min).
  - Moderate liver failure (Child-Pugh B). In severe liver failure should not be administered.

- **Contraindications**
    - Hypersensitivity to the active substance or excipient
    - Tuberculosis, severe and active infection such as sepsis or opportunistic infection
    - Severe liver failure
    - Pregnancy or lactation
    - Not recommended for use in patients with a lymphocyte count of <750 cells/mm3; a neutrophil count of <1000 cells/mm3 or hemoglobin levels of <9g/dl.

- **Side effects**
    - *Very frequent* (>1/10): nasopharyngitis
    - *Frequent* (<1/10): pneumonia, herpes zoster flu, UTI, sinusitis, bronchitis, leukopenia, anemia, insomnia, headache, dyspnea, cough, vomiting, diarrhea, nausea, fatigue, elevated transaminases.
    - *Infrequent* (<1/100): sepsis, tuberculosis, cellulitis, bacterial pneumonia, viral gastroenteritis, non-melanoma skin cancer, lymphopenia, neutropenia, paresthesias, hepatic steatosis, pruritus, elevated transaminases.
    - *Very rare* (<1/1000): tuberculosis of central nervous system, meningitis, urosepsis and atypical mycobacterial infection.

- **Analytical control**

  A blood test should be done before starting treatment with tofacitinib, after 4-8 weeks of treatment, and then every 3 months to determine if there is a low white or red blood cell count. Periodic monitoring of liver enzymes should also be done.

2. JUSTIFICATION

RA is a chronic, disabling disease with significant social and economic costs and psychological repercussions, as well as a reduced quality of life. (1) The disease can lead to a reduction in survival of 5 years and a high rate of disability (20-30%) (49) and an incapacity for work of up to 5% of the incapacities for work in Spain. (50)

It is a disease with a prevalence of 0.5% in our country, with an incidence of 8.3 cases/100000 inhabitants.(51)

From the appearance of the biological therapy (anti-TNF drugs), the control of the disease advanced being reflected in the improvement of the symptoms and the progression of the joint damage. Its recommendation is to give them as a second line of treatment but in several articles it is observed that a third of patients with anti-TNF do not respond to it. Faced with this, there are scientific data that support a second anti-TNF (switching) or change the therapeutic target (52),because half of the patients with an active and evolved RA, after a first failure with anti-TNF, do not achieve a good therapeutic response (25) to the second anti-TNF, either due to lack of tolerability or due to resistance to the pharmacological treatment with the generation of antidrug antibodies (29)

There is little guidance in choosing the next treatment. The scientific literature, based on retrospective studies of large registries, accepts both switching to another anti-TNF and changing the therapeutic target. There are observational studies that support that the change of therapeutic target seems to be better. (35,37)

The only controlled trial that compares the two strategies (36) has its limitations (40% of patients did not take MTX), but it also seems to be more effective to switch to a non-TNF biological therapy when the first anti-TNF fails.

Tofacitinib, an inhibitor of Janus Kinasa, a new therapeutic target for the treatment of RA, has been shown to be effective, in combination with MTX, when the first anti-TNF fails.(34)

We have performed this study because we believe that a change of therapeutic objective with a janus kinase inhibitor (Tofacitinib) when a first anti-TNF fails may be more effective than switching to a second anti-TNF.

3. HYPOTHESIS

3.1. MAIN HYPOTHESIS

Tofacitinib, a JAK inhibitor, is a new therapeutic target that has shown efficacy to anti-TNF failure. So we thought it might be more effective than a second anti-TNF in the treatment of patients with active RA that they have had failure at first anti-TNF treatment.

3.2. SECONDARY HYPOTHESIS

JAK inhibitors greatly influence acute phase reactants. Using the indices in which these parameters have great weight (DAS28), a higher rate of tofacitinib improvement could be expected. Therefore we will see that there is a good correlation between DAS28 and SDAI, CDAI and HAQ; which have more clinical weight.

4. OBJETIVES

4.1. MAIN OBJECTIVE

To compare the efficacy of tofacitinib versus a second anti-TNF drug in the treatment of patients diagnosed with active RA that does not respond to first anti-TNF by the proportion of good/moderate response rates according to EULAR at 6 months of treatment.

4.2. SECONDARY OBJECTIVES

To compare, in the treatment of patients with active RA that do not respond to first anti-TNF drug:

1. Low disease activity reflected in DAS28-ESR
2. Low disease activity reflected in SDAI
3. Low disease activity reflected in CDAI
4. Improvement of HAQ score

5. METHODOLOGY

5.1. STUDY DESIGN

We will carry out a multicentric, open-label, pragmatic and prospective randomized clinical trial with parallel groups.

Patients with insufficient response to a first anti-TNF drug will be randomly assigned in a 1:1 ratio to receive a JAK inhibitor (tofacitinib) or a second anti-TNF agent.

The duration of the study will be a follow-up of one year to do control in third month, sixth month and twelfth month. With a recruitment period of one year and half.

5.2. STUDY SUBJECTS

The target population of this study are patients with active RA and with insufficient response to a first anti-TNF drug in Catalonia.

Patients will be informed at the consulting rheumatology room by the study.

5.2.1. Inclusion criteria

1- Patients≥18 years old, diagnosed of RA according to the 1987 ACR criteria.
2- Active RA with insufficient response to treatment with anti-TNF drug (defined as a score of DAS28-ESR >3.2).
3- Stable dose of DMARDs (MTX) within 4 weeks of enrollment.
4- Stable dose of oral corticoesteroids of 15 mg/day or less of equivalent prednisone within 4 weeks before enrollment.
5- Informed written consent. [ANNEX 4]

5.2.2. Exclusion criteria

1- Discontinuation of the first anti-TNF agent due to an adverse event.
2- Previous treatment with 2 or more anti-TNF agents.
3- Previous treatment with non-TNF-targeted biologic therapies.
4- Contraindication to anti-TNF agents and/or Jak-inhibitor, tofacitinib.
5- Treatment in monotherapy with other DMARDs different of MTX.

5.3. SAMPLING AND SAMPLE SIZE

5.3.1. Sampling

Our sampling will consist in a non-probabilistic consecutive sampling because all available patients being visited in Catalan hospitals with a Rheumatology service will be invited to accept the study proposal that meets the inclusion and exclusion criteria.

5.3.2. Sample size

To calculate the sample size we used the GRANMO software for the efficacy of treatment, our main dependent variable, measured as the proportion of responders to each drug, tofacitinib or an anti-TNF drug. The group ratio will be 1:1.

Accepting alpha risk of 0.05 and beta risk of 0.2 in a bilateral contrast, we need 188 patients in the first group and 188 patients in the second group, with 376 patients in total; to detect a statistically significant difference between two proportions. We hope to obtain that at least 65% of patients in group A will have an effective response, while in group B only 50% will achieve it.
A follow-up loss rate of 10% has been estimated.

5.4. VARIABLES

5.4.1. Independent variables

The independent variables of our study will be the administration of the second-line drugs. First group will receive an oral pill of tofacitinib plus methotrexate, this group will be identified as the drug A. The second group will receive an injection of any anti-TNF drug plus methotrexate, this group will be identified as the drug B.
These are considered dichotomous qualitative variables.

5.4.2. Dependent variables

The main dependent variable of this study is the efficacy of the treatment as the proportion of patients who have a good/moderate EULAR response that it will be measured as the response to treatment [Table 2] according to Disease Activity Score (**DAS28-ESR**).
The range of possible values is 0-9.4. DAS can evaluate the activity of the disease [Table 1] and the response to treatment [Table 2].
As it is about advanced RA in our study it is difficult for patients to reach remission of the disease, so we will define that the treatment will be effective when the patient presents a DAS-28 of good or moderate response to treatment, or a low or moderate activity.
Both dependent variables are politomous qualitative variables.

5.4.2.1. Secondary dependent variables

- **SDAI** (Simplified Disease Activity Index)(11) [Annex 1]
- **CDAI** (Clinical Disease Activity Index)(12) [Annex 2]

- **HAQ** (Health Assessment Questionnaire)(13): is a functional assessment questionnaire with 20 items that assess self-perceived physical disability in order to carry out various basic activities of daily life grouped into eight areas. [Annex 3].

The secondary dependent variables are politomous qualitative variables.

5.4.3. Covariables

As the sample will be randomized, there will be no confounders.
But as the randomization will be done in each hospital, there can be a difference between hospitals so the possible residual confusions will be controlled.
We will collect the baselines characteristics of patients to obtain epidemiological and clinical data at the beginning of the study, such as age, gender, disease duration, evaluation of disease (baseline DAS28-ESR and HAQ score), rheumatoid factor, anticyclic citrullinated peptide positivity, number of previous synthetic DMARDs taken, previous anti-TNF drug and the reason to ineffectiveness of anti-TNF drug.

5.5. STUDY INTERVENTIONS

5.5.1. Randomization

The participants of the study will be divided in two groups with a randomized electronic procedure.

- Group A: this group will receive an oral pill of tofacitinib plus methotrexate, daily.
- Group B: this group will receive an injection of any anti-TNF drug plus methotrexate, according to anti-TNF but it isn't daily. The choice of the anti-TNF drug will be at the physician's discretion.

The randomization will do in each hospital.

5.5.2. Study interventions

After the recruitment of patients who are included in inclusion criteria, we will distribute in two groups:

- Group A: this group will receive an oral pill of tofacitinib of 5mg, and in the next 12 hours other pill of 5mg, in total 10mg per day.

- Group B: this group will receive an injection of anti-TNF drug(53) at the doctor's discretion:

DRUG	DOSAGE
Infliximab	It's administered as an intravenous infusion at a dose of between 3 and 5 mg/kg (depending on body weight) at weeks 0, 2 and 6.
Etanercept	50 mg once a week or 25 mg twice a week as a self-administered subcutaneous injection.
Adalimumab	40 mg every two weeks as a self-administered subcutaneous injection.
Golimumab	It's administered as an intravenous infusion at a dose of 2 mg/kg (depending on body weight) at weeks 0 and 4
Certolizumab	400mg, in two times (200mg and 200mg) as a self-administrated every week in weeks 0, 2 and 4.

5.6. DATA COLLECTION

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

The next step, the patients included in the inclusion criteria, will receive the information sheet of this clinical trial and if they agree with our study, they will sign the informed consent document. [ANNEX 4]

Firstly, we will collect the baseline characteristics of the patients [Table 5]:

- Age
- Gender
- Disease duration
- Evaluation of disease (baseline DAS28-ESR and HAQ score, and radiographic image)
- Number of painful joints

- Number of swollen joints
- Erythrocyte sedimentation rate in mmHg; C-reactive protein in mg/dL
- Rheumatoid factor positive if >15U/ml by nephelometry and anticyclic citrullinated peptide positive if >20 U/ml by enzyme-immunoassay technique.
- Side effects
- Dose of prednisone 4 previous weeks.
- Dose of MTX 4 previous weeks.
- Previous anti-TNF drug and treatment time with the first anti-TNF.
- Reason to ineffectiveness of anti-TNF drug.

Also, we will collect the clinical information: allergies, other pathologies and concomitant treatment. And they will do a blood test with white and red blood cell count, and analysis the liver and renal function.

Then, the enrolled patients will include randomly in the group A or in the group B. And, at week 12, week 24 and 52 week (38), the rheumatologists will measure the efficacy of the treatment mainly according to Disease Activity Score (DAS28-ESR), but also, we could measure it according to CDAI, SDAI and HAQ.

The therapeutic objective must be attained, at least partially, at 3 months and, at the most, at 6 months, as the activity at 3 and 6 months makes it possible to predict the response in the medium and long term.

Table 5. Data collection

	WEEK 0	WEEK 12	WEEK 24	WEEK 52
Age	X			
Gender	X			
Years with RA	X			
DAS28-ESR SDAI/CDAI HAQ	X	X	X	X
Painful joints	X	X	X	X
Swollen joints	X	X	X	X
ESR + CRP	X	X	X	X
RF + ACCP	X	X	X	X
Side effects	X	X	X	X
Dose of MTX 4 previous weeks	X			
Dose of prednisone 4 previous weeks	X			
First anti-TNF drug	X			
Reason to ineffectiveness of anti-TNF drug	X			
Concomitant treatment	X	X	X	X
Blood count and liver and renal function analysis	X	X	X	X
Side effects		X	X	X

6. STATISCAL ANALYSIS

6.1. Descriptive analyses

We will summarize the dependent variables, both primary and secondary, using proportions expressed in percentages; for the two groups A and B, the same will be done for the rest of 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 and interquartile range (IQR) when they are discrete variables; for the two groups (A and B).

6.2. Bivariate inference

We will contrast the difference in proportions of the dependent variables, the main and secondary variables, and of the qualitative covariates between groups A and B by means of chi-square and Fisher's exact test.

We will contrast the difference of means and means of the covariates between groups A and B by means of the student T and the Mann-Whitney U, respectively.

6.3. Multivariate analyses

We will evaluate the efficacy of the drugs, tofacitinib and anti-TNF, using logistic regressions where the response variables will be the indexes of evaluation of the response to treatment (DAS28, SDAI, CDAI and HAQ). The explanatory variable of interest will be tofacitinib (anti-JAK drug) and anti-TNF drugs, adjusting for covariates.

7. WORK PLAN AND SCHEDULE OF EVENTS

We will recruit 376 in the different hospitals of Catalonia, so the time estimated to the recruitment will be one year and half; with individual controls for one year. We think that the small hospitals can yield fewer patients than large hospitals.

Healthcare personnel involved include: the rheumatologists of each hospital as the principal investigators of our study but also, we need pharmacists and nursing staff as co-investigators; and one statistician to analyse the results.

7.1. STAGE 1: COORDINATION AND REDACTION OF STUDY PROTOCOL

1) The first step is that of protocol elaboration. This is developed via the formulation of study aims and identifications of study variables suitable for answering the formulated research hypothesis. In order to do this, an extensive literature search will be performed. Finally, the methodology of the study will be established.
2) In step two the protocol will be evaluated by the relevant committees (CEIC) and pertinent administrative authorizations obtained (AEMPS). This will be done before the start of the trial.
3) Step three will involve organizational meetings in order to coordinate all the participating hospitals. Hospitals will be asked to notify when they identify a patient in their hospitals that may meet the inclusion criteria.
4) During step three, a chronogram will be elaborated. This will happen after mutual agreement of all parties involved.

   The estimated duration of this phase is 5 months.

7.2. STAGE 2: SAMPLE COLLECTION, FOLLOW-UP VISITS AND DATA COLLECTION

The second phase of the study will include:

1. Recruitment of patients using a consecutive sampling if they meet the inclusion and exclusion criteria and if the informed consent is available.
2. Collecting the baseline characteristics of the enrolled patients.
3. Study intervention: patients will be randomly distributed in one of the groups of the study, and then rheumatologists will administer one of the two drugs according to the group A or B.
4. Follow-up visits: they will be realized in week 12, 24 and 52 to evaluate the efficacy of the treatments according to the different indexes.
5. Collection of data: rheumatologists will collect the information of each visit.
6. Coordination meetings: the principal investigators will meet in order to assess that the protocol is well executed and to determine if they need to modify some procedures.

This phase will involve both investigators and co-investigators, and the estimated durantion of this stage is 18 months according to the time needed to recruit 376 patients for our study.

7.3. STAGE 3: STATISTICAL ANALYSIS AND INTERPRETATION OF RESULTS

This phase will consist of data processing and statistical analysis, and is expected for 4 months. This phase will involve the investigators and the statistician.

After the intervention and final statistical analysis are completed, results will be interpreted and conclusions will be drawn.

7.4. STAGE 4: PUBLICATION OF RESULTS

During this last phase, the results of the study will be prepared for publication. This is expected to take two months, and will be done by the investigators. The results will be summarized in format of scientific papers and will be sent to medical journals for their publication.

7.5. CHRONOGRAM

STAGES	2018		2019												2020												2021											
	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
STAGE 1: Coordination and redaction of study protocol																																						
- Scientific research and protocol elaboration																																						
- AEMPS and ethical approval (CEIC)																																						
- Initial coordination meeting																																						
SATGE 2: Sample collection, follow-up visits and data collection																																						
- Recruitment, data collection and study interventions																																						
STAGE 3: Statistical analysis and interpretation of results																																						
- Statistical analysis																																						
- Analysis and interpretationof the results																																						
STAGE 4: Publication of results																																						
- Final article elaboration																																						
- Results publication																																						

8. ETHICAL CONSIDERATIONS

This clinical trial follows the medical ethics requirements stated by the World Health Association in the Declaration of Helsinki (1964) about the Ethical Principles for Medical Research Involving Human Subjects.

Once this protocol will be finished, it will be sent to the Clinical Research Ethics Comitte (CEIC) in order to be evaluated and approved. According to the "Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos" (54) the approbation of the protocol by CEIC is mandatory to start clinical research. Moreover, it will be also sent to the Asociacion española de medicamentos y productos sanitarios (AEMPS) and its 'Ensayos Clínicos con Medicamen'os' (ECM) portal to authorize it. After its authorization, an application for a registry number to the European Union Drug Regulating Autorities Clinical Trials (EudraCT) will be also checked.

As it is a low level intervention clinical trial, because both groups of drugs are authorized for commercialization and there are scientific data on their safety and efficacy; no specific insurance is necessary for the possible consequences.

It only needs the liability policy of the centers in which the study is carried out.

Permission to perform this study will be asked to the direction of our hospitals.

Patients will only be enrolled in our study if the informed consent is available. In order to obtain it, patients will receive the information sheet of our clinical trial and then if they agree with it, they will sign the informed consent document [ANNEX 4]

This clinical trial guarantees that all the information obtained will be confidential and anonymous according to the "Ley orgánica 3/2018, de 5 diciembre, de Protección de datos personales y garantía de los derechos digitales".

9. STUDY LIMITATIONS

- The main limitation of our study is the lack of blinding of participants because it should be at the discretion of the physician the free choice of the second anti-TNF drug, as her/his usual clinical practice.
- Treatment adherence might have differed between the 2 groups because the anti-TNF drugs were self-injected by patients and it can be more painful than tofacitinib that is oral pill.
- This study is multicentric, so it could create variability because in each hospital has a specific method. But being a multicentric study in different hospitals of Catalonia, the results could be more generalizable.
- Due to the size of the sample, we will not be able to take conclusions by comparing every second anti-TNF, because we would need a larger sample size.

10. BUDGET

EXPENSES	**COSTS (€)**
1. PERSONAL EXPENSES (Staff) a. Rheumatologists (300€/patient) b. Pharmacists c. Nursing staff	112.800€
2. EXECUTIVE EXPENSES	
Data management 400h/30€	12000€
Statistician (ST) 100h/35€	3500€
Insurance 20€/patient	7520€
3. PUBLICATION AND DISEMINATION EXPENSES	
Scientific publications	1500€
Scientific publication (x2, both protocol and results publication)	1500€
Travel transportation, accommodation, meetings	5000€
TOTAL COST	**143.820€**

11. IMPACT ON THE HEALTHCARE

Rheumatoid arthritis can cause joint deformity if it is not treated correctly or if treatment is not effective and the arthritis reaches the advanced stage, it can also affect systematically.

If the results of the study showed superior efficacy for tofacitinib, in clinical practice it might be a good option to change therapeutic target when there is failure to the first anti-TNF drugs.

If the study results showed no difference between tofacitinib and a second anti-TNF drug after failure of the first anti-TNF drug, the choice of drug would be at the physician's discretion. So, nowadays good clinical practice is being performed.

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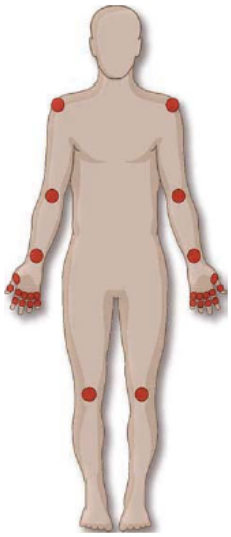
13. ANNEXES

ANNEX 1. SDAI

Simple Disease Activity Index (SDAI)

Joint	Left		Right	
	Tender	Swollen	Tender	Swollen
Shoulder				
Elbow				
Wrist				
MCP 1				
MCP 2				
MCP 3				
MCP 4				
MCP 5				
PIP 1				
PIP 2				
PIP 3				
PIP 4				
PIP 5				
Knee				
Total	Tender:		Swollen:	



Patient Global Assessment of Disease Activity

Considering all the ways your arthritis affects you, rate how well you are doing on the following scale:

Very Well 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 Very Poor

Your Name_____ **Date of Birth** _____ **Today's Date** _____

Provider Global Assessment of Disease Activity

Very Well 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 Very Poor

How to Score the SDAI

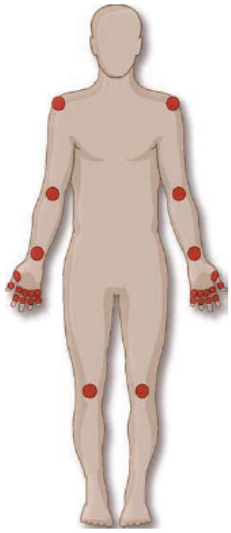
Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
C-reactive protein (mg/dL)	(0-10)	
Add the above values to calculate the SDAI score	**(0-86)**	

SDAI Score Interpretation	
0.0 – 3.3	Remission
3.4 – 11.0	Low Activity
11.1 – 26.0	Moderate Activity
26.1 – 86.0	High Activity

ANNEX 2. CDAI

Clinical Disease Activity Index (CDAI)

Joint	Left		Right	
	Tender	Swollen	Tender	Swollen
Shoulder				
Elbow				
Wrist				
MCP 1				
MCP 2				
MCP 3				
MCP 4				
MCP 5				
PIP 1				
PIP 2				
PIP 3				
PIP 4				
PIP 5				
Knee				
Total	Tender:		Swollen:	



Patient Global Assessment of Disease Activity

Considering all the ways your arthritis affects you, rate how well you are doing on the following scale:

Very	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	Very
Well	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	Poor

Your Name_____ **Date of Birth** _____ **Today's Date** _____

Provider Global Assessment of Disease Activity

Very	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	Very
Well	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	Poor

How to Score the CDAI

Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
Add the above values to calculate the CDAI score	**(0-76)**	

CDAI Score Interpretation	
0.0 – 2.8	Remission
2.9 – 10.0	Low Activity
10.1 – 22.0	Moderate Activity
22.1 – 76.0	High Activity

ANNEX 3. HAQ

Versión Española del Health Assessment Questionnaire (HAQ)

Traducida y adaptada por J. Esteve-Vives, E. Batlle-Gualda, A. Reig y Grupo para la Adaptación del HAQ a la Población Española

	Durante la <u>última semana</u>, ¿ha sido usted capaz de...	Sin dificultad	Con alguna dificultad	Con mucha dificultad	Incapaz de hacerlo
Vestirse y asearse	1) Vestirse solo, incluyendo abrocharse los botones y atarse los cordones de los zapatos?	☐	☐	☐	☐
	2) Enjabonarse la cabeza?	☐	☐	☐	☐
Levantarse	3) Levantarse de una silla sin brazos?	☐	☐	☐	☐
	4) Acostarse y levantarse de la cama?	☐	☐	☐	☐
Comer	5) Cortar un filete de carne?	☐	☐	☐	☐
	6) Abrir un cartón de leche nuevo?	☐	☐	☐	☐
	7) Servirse la bebida?	☐	☐	☐	☐
Caminar	8) Caminar fuera de casa por un terreno llano?	☐	☐	☐	☐
	9) Subir cinco escalones?	☐	☐	☐	☐
Higiene	10) Lavarse y secarse todo el cuerpo?	☐	☐	☐	☐
	11) Sentarse y levantarse del retrete?	☐	☐	☐	☐
	12) Ducharse?	☐	☐	☐	☐
Alcanzar	13) Coger un paquete de azúcar de 1 Kg de una estantería colocada por encima de su cabeza?	☐	☐	☐	☐
	14) Agacharse y recoger ropa del suelo?	☐	☐	☐	☐
Prensión	15) Abrir la puerta de un coche?	☐	☐	☐	☐
	16) Abrir tarros cerrados que ya antes habían sido abiertos?	☐	☐	☐	☐
	17) Abrir y cerrar los grifos?	☐	☐	☐	☐
Otras	18) Hacer los recados y las compras?	☐	☐	☐	☐
	19) Entrar y salir de un coche?	☐	☐	☐	☐
	20) Hacer tareas de casa como barrer o lavar los platos?	☐	☐	☐	☐

ANNEX 4. INFORMED CONSENT DOCUMENT

FULL DE CONSENTIMENT INFORMAT PELS PACIENTS

Apreciat/da:

Vosté presenta una artritis reumatoide; una malaltia crònica reumàtica que pot danyar de manera progressiva les articulacions. Després de provar un primer anti-TNF, no ha millorat clínicament, per el que no ha tingut bona resposta al tractament.

En aquest estudi intentarem mirar la eficàcia d'una nova diana terapèutica, els anti-JAK, concretament el tofacitinib; a una artritis reumatoide activa que ha fet fallo al primer anti-TNF.

Vosté pot negar-se a participar en l'estudi i no afectará en absolut al tractament que se li realitzarà ni al seu seguiment posterior.

La participació en aquest estudi no suposa la realització de fer proves extraordinàries, simplement entrar al grup A (amb tractament amb tofacitinib) o al grup B (segon anti-TNF), a més dels procediments habituals de valoració clínica i analítica per a saber la evolució de la resposta al tractament.

Si acepta participar en l'estudi, li garantim la confidencialitat de les seues dades personals ('Ley Orgánica de Protección de Datos de Caràcter personal 3/2018') i així com els resultats de l'estudi.

Jo, _____(nom i cognoms del participant), accepte participar en l'assaig clínic sobre l'ús de tofacitinib o anti-TNF en el tractament de la artritis reumatoide activa que ha tingut una inadecuada resposta al primer anti-TNF, i confirmo que:

- He llegit tota la informació que se m'ha entregat sobre el projecte.
- He tingut l'oportunitat de preguntar els dubtes sobre l'estudi.
- He rebut respostes satisfactòries a les meves preguntes.
- He rebut suficient informació sobre aquest projecte.
- He entès els possibles riscos associats a la participació en aquest projecte.

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

Comprenc que la participació es voluntària

Comprenc que puc retirar-me de l'estudi:

- Quan vulgui.
- Sense haver de donar explicacions.
- Sense alteracions amb les meues assistències sanitàries posteriors.

Estic informat/da de:

- La existènica d'un fitxer automatitzat de dades de carácter personal.
- La informació podrà ser utilitzada exclusivament per a finalitats científiques amb confidencialitat.
- El fitxer estarà en mans de l'investigador principal i tinc dret a l'accés, rectificació, cancel·lació i oposició.

Accepto lliurement participar en aquest estudi.

Signatura del pacient

Signatura de l'investigador

Lloc i data: _____, ____ de _____ del 20__

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo, _____, revoco el consentiment prèviament signat per la participació en l'assaig clínic especificat a dalt.

Signatura del pacient

Signatura de l'investigador

Lloc i data: _____, ____ de _____ del 20__