BMJ Open

Efficacy, safety and cost-effectiveness of methotrexate, adalimumab or their combination in non-infectious non-anterior uveitis: a protocol for a multicentre, randomised, parallel three arms, active-controlled, phase III open label with blinded outcome assessment study

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To cite: Rivas AB, Lopez-Picado A, Calamia V, *et al*. Efficacy, safety and cost-effectiveness of methotrexate, adalimumab or their combination in non-infectious non-anterior uveitis: a protocol for a multicentre, randomised, parallel three arms, active-controlled, phase III open label with blinded outcome assessment study. *BMJ Open* 2022;**12**:e051378. doi:10.1136/bmjopen-2021-051378

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-051378).

Received 18 March 2021
Accepted 22 February 2022

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ABSTRACT

Introduction Non-infectious uveitis include a heterogeneous group of sight-threatening and incapacitating conditions. Their correct management sometimes requires the use of immunosuppressive drugs (ISDs), prescribed in monotherapy or in combination. Several observational studies showed that the use of ISDs in combination could be more effective than and as safe as their use in monotherapy. However, a direct comparison between these two treatment strategies has not been carried out yet.

Methods and analysis The Combination THerapy with mEthotrexate and adalImumAb for uveitis (CoTHEIA) study is a phase III, multicentre, prospective, randomised, single-blinded with masked outcome assessment, parallel three arms with 1:1:1 allocation, active-controlled, superiority study design, comparing the efficacy, safety and cost-effectiveness of methotrexate, adalimumab or their combination in non-infectious non-anterior uveitis. We aim to recruit 192 subjects. The duration of the treatment and follow-up will last up to 52 weeks, plus 70 days follow-up with no treatment. The complete and maintained resolution of the ocular inflammation will be assessed by masked evaluators (primary outcome). In addition to other secondary measurements of efficacy (quality of life, visual acuity and costs) and safety, we will identify subjects' subgroups with different treatment responses by developing prediction models based on machine learning techniques using genetic and proteomic biomarkers.

Strengths and Limitations of this Study

- ► This is the first randomised controlled study designed to compare the efficacy of combination therapy versus monotherapy for the treatment of non-infectious uveitis in subjects with no previous immunosuppressive treatment.
- ► We have chosen quite a strict outcome (the requirement of a maintained controlled inflammation), more likely related to long-term outcomes (such as structural damage) and to patient-reported outcome measures.
- ► Despite the previous point, our primary efficacy outcome is still a surrogate marker: the achievement of this outcome does not have necessarily to translate in an improvement of outcomes more important for the patient, such as quality of life or disability.
- ► The requirement to control the inflammatory process early (by week 16) may cause an underestimation of drug efficacy, as it could take more time to control the inflammation but be associated with a similar long-term prognosis.
- ► The lack of masking could introduce bias, although treatment characteristics and proven effectivity in non-infectious uveitis, the duration of the trial (up to 52 weeks) and the need for biweekly subcutaneous injections of one of the drugs (adalimumab), we consider unpractical for the subject the use of placebo in the present trial.

Ethics and dissemination The protocol, annexes and informed consent forms were approved by the Reference Clinical Research Ethic Committee at the Hospital Clínico San Carlos (Madrid, Spain) and the Spanish Agency for Medicines and Health Products. We will elaborate a dissemination plan including production of materials adapted to several formats to communicate the clinical trial progress and findings to a broad group of stakeholders. The promoter will be the only access to the participant-level data, although it can be shared within the legal situation.
Trial registration number 2020-000130-18; NCT04798755.

INTRODUCTION

Uveitides are potentially sight-threatening diseases:[1] worldwide, they represented up to 10% of causes of blindness (almost 4 million people).[2] Furthermore, in the European Union and the USA, after diabetic retinopathy, uveitides represent the second major treatable cause of blindness in those 20–65 years of age[3] (up to 10% of cases of blind registrations[3–6]). Additionally, a high percentage of patients suffer from uveitis-related complications, visual impairment[4 7 8] and a negative impact in quality-of-life (QoL).[9 10] Considering their higher prevalence in young to middle-aged adults,[11 12] uveitides cause an important economic, social and personal burden.[5 13–16]

The correct management of non-infectious uveitis (NIUs) is essential for preserving visual function and avoiding ocular and extra-ocular morbidity.[17] Although glucocorticoids (GCs) are the mainstay of treatment,[18] under certain circumstances, adding immunosuppressive drugs (ISDs) is needed to achieve a sustained control of the inflammatory process.[19] Several ISDs are used in the standard of care, such as methotrexate (MTX) and biological agents.[19–21]

Regarding MTX, its effectiveness in NIU has been assessed in two randomised clinical trials, compared with mycophenolate mofetil (MMF): Rathinam *et al*[22] observed that 69% and 47% of patients treated with MTX and MMF, respectively, achieved complete control of inflammation and daily oral GCs dosage ≤10 mg at 5 and 6 months (p=0.09). In a second trial,[23] randomising 200 patients, the percentage of subjects achieving a similar outcome was 67% and 57% for MTX and MMF, respectively (p>0.05), with similar tolerability. Regarding safety, adverse events (AEs) are generally mild and discontinuations due to serious adverse events (SAEs) are less common than for most ISDs,[24 25] translating it in higher retention rates.[26 27]

Regarding adalimumab (ADA), its effectiveness in NIU has been shown in two randomised controlled trials.[28 29] The VISUAL I study[28] compared ADA with placebo in 217 NIU patients with active uveitis despite ≥10 mg/day of systemic GCs. Based on the cumulative number of subjects with treatment failure in each visit, by week 25 (about 6 months), 31 of 107 (29%) subjects in the placebo group and 62 of 110 (56%) subjects in the ADA group had not suffered a treatment failure. By 50 weeks, the numbers were reduced to 24 (22%) and 51 (46%), respectively. Regarding safety, many of the AEs are sufficiently mild to not require discontinuation, such as injection site pain and antidrug antibodies formation,[19 30 31] reflecting in a high retention rate.[32] Regarding SAEs, there was no association with higher risk in a recent meta-analysis,[33] compared with placebo or synthetic ISDs. However, ADA was associated with a higher risk of treatment discontinuation due to SAEs. One of the most important ADA's AEs are infections. However, a previous meta-analysis reported that the absolute risk was low (0.036% with TNF-alpha inhibitors vs 0.017% with placebo),[34] which probably does not represent a clinically important constraint on the use of these agents. Finally, ADA has not showed an association with a higher risk of malignancy.[33]

Although ISDs are usually used in monotherapy in uveitis, several observational studies have shown that in 21%–52% of NIU patients, the use of ISDs in monotherapy was unable to achieve a sustained control of the inflammatory process.[27 35–37] Furthermore, other studies have provided evidence that the combination of two or more ISDs could offer advantages in terms of effectiveness and tolerability,[38–41] in conditions such as Birdshot retinochoroidopathy,[38] serpiginous choroiditis,[39 40] Vogt-Koyanagi-Harada syndrome (VHK),[42 43] ocular Behçet's disease,[44 45] JIA associated uveitis,[46] sympathetic ophthalmia[47] and intermediate uveitis.[48] Regarding the beneficial of combining both MTX and ADA, several RCTs have provided evidence in other immune-mediated inflammatory diseases (IMIDs).[49] In NIU, this combination was tested in children with Juvenile Idiopathic Arthritis-associated Uveitis and a previous failure to MTX monotherapy.[50] The combination of MTX and ADA was more effective compared with MTX and placebo, although it was associated with a higher proportion of AEs (88% vs 83% of patients) and SAEs (22% vs 7%).

Despite all the evidence, a direct comparison between combination and monotherapy has not been tested yet, although some groups have adopted the use of combination therapy as the initial ISD treatment for particular conditions.[51]

There are currently no tools able to predict the response or non-response to ISDs in those NIUs needing immunosuppression, as there is marked interpersonal variation in their efficacy and toxicity. Response to the first-line ISD treatment could be an important predictor of long-term outcomes, as the continuous or repeated eye inflammation could increase the risk of structural permanent damage, leading to blindness, disability and deterioration in the QoL. Therefore, starting on the right ISD is likely a key factor in achieving a better and more cost-effective therapy, and improving the optimal allocation of healthcare resources. To achieve these aims, objectively measured and evaluated characteristics (biomarkers[52]) are required, in addition to the identification of clinical features associated with the outcomes of interest.

METHODS AND ANALYSIS

Study overview

The Combination THerapy with mEthotrexate and adalImumAb for uveitis (CoTHEIA) study is a phase III, multicentre, prospective, randomised, single-blinded with masked outcome assessment, parallel three arms

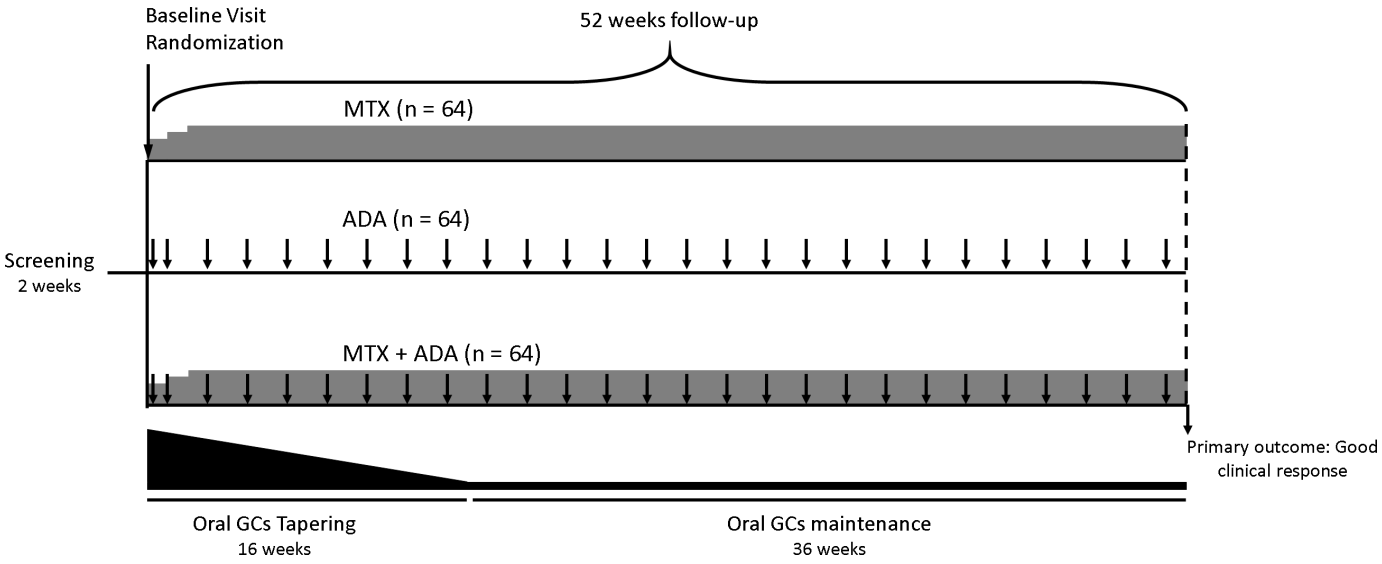

Figure 1 Overview of the study timeline and interventions. ADA, adalimumab; MTX, methotrexate.

with 1:1:1 allocation, active-controlled, superiority study design, comparing the efficacy, safety and cost-effectiveness of MTX, ADA or their combination in non-infectious non-anterior uveitis. The duration of the treatment and follow-up will last up to 52 weeks. A 70-day follow-up clinic visit or phone call will take place to assess safety after the last study drug dose. Figure 1 provides an overview of the study timeline and interventions.

Objectives and outcome variables

The trial main hypothesis is that the use of combination therapy with MTX and ADA will be more effective in inducing and maintaining ocular inflammatory inactivity than either drug given in monotherapy.

The *primary efficacy objective* is to establish which treatment strategy results in a higher proportion of subjects achieving a complete and maintained resolution of the ocular inflammation, on an intent to treat basis. The *primary efficacy outcome* will be the proportion of patients achieving a *Good Clinical Response* between the combination therapy arm and the single ISD arms. This outcome is defined as a complete resolution of the ocular inflammatory signs (including active chorioretinal lesions, active retinal vascular inflammation, uveitis macular oedema, presence of anterior chamber cells and presence of vitreous haze), achieved within the first 16 weeks of the study and maintained during follow-up until the end of the study (week 52); furthermore, there must not be a treatment failure due to safety or intolerability; the subject must adhere to the initial (up to week 16) oral GCs tapering protocol; all study visits from baseline to 16 weeks must be completed and at the final visit (week 52), the subject must be treated with up to 7.5 mg/day of oral prednisone (or equivalent) and up to two times a day of prednisolone acetate 1% (or equivalent). The *secondary efficacy objectives* and outcomes variables can be found at table 1.

Security-related objective will establish which treatment strategy has better tolerability. Safety outcomes will be collected in the form of AEs, physical examination and laboratory tests throughout the treatment period and up to 70 days after the last dose in this study. Gender of the subjects will be taken into account.[53]

Pharmacogenetic and proteomic-related objectives include identifying groups of subjects more likely to respond to the different treatment strategies, using genetic and proteomic biomarkers. For the former, subjects will be genotyped for known and validated genetics single nucleotide polymorphisms (SNPs) associated with a MTX[54] and ADA[55] response in different IMIDs. For the latter, a Discovery (shotgun proteomic analysis), Verification (targeted proteomics using multiple reaction monitoring (MRM) test) and Validation (antibody-based microarrays absolute quantification tests) phases will be carried out, following optimised protocols and procedures.[56–61]

Finally, a *Biobank substudy-related objective* will be carried out with the aim of boosting the translational research in the field of NIUs, by creating a collection of blood-derived samples (serum, plasma, total blood RNA and DNA) from the participant subjects in order to advance in the identification and validation of biomarkers associated with treatment response or deepen in the pathophysiology of these conditions.

Settings and eligibility

The study population encompasses subjects diagnosed with non-infectious intermediate, posterior or panuveitis with active disease within 180 days before the start of the study (baseline visit), and either a documented failure to systemic or local GCs, or a chronic disease requiring GC-sparing ISD treatment. Main inclusion and exclusion criteria can be found in table 2.

Subjects will be recruited from 16 Spanish academic hospitals located in different regions of Spain (Galicia,

Table 1 Efficacy-related secondary objectives and outcome variables

Objective	Outcome variable
To compare the fraction of subjects who achieve a complete inflammatory ocular inactivity by week 16	Complete abrogation of the ocular inflammatory signs, which is achieved within the first 16 weeks of the study, no treatment failure due to safety or intolerability; compliance with the initial (up to week 16) oral GCs tapering protocol, and completion of all study visits from baseline to 16 weeks
To compare several Patient-Reported Outcomes Measures (health-related and vision-related quality of life, anxiety and depression) between treatment strategies	EuroQuol 5D-5L Visual Functioning Questionnaire-25 Hospital Anxiety and Depression Scale
To compare the presence of the clinical components of the Good Clinical Response variable between treatment strategies during follow-up	Active chorioretinal lesions; active retinal vascular inflammation; macular oedema; ACC; vitreous haze and loss of CVA secondary to inflammation at baseline, week 16, week 52 and relapse visit
To compare the time to relapse after week 16 between treatment strategies	The time to inflammatory relapse between groups, defined as the time from visit 16 weeks until end of the study, loss of follow-up or appearance of at least one ocular inflammatory manifestation, in those individuals achieving a Good Clinical Response by visit 16 week
To compare the evolution of visual acuity during follow-up	Best-corrected visual acuity (BCVA) during follow-up
To compare the development of anti-adalimumab antibodies during the follow-up, between those subjects treated with monotherapy and combination therapy	Assessment of anti-ADA antibodies (AAA) at week 15, 27, 51 and relapse
To assess the cost-utility and cost-effectiveness from both a Health System and a Societal perspective of the combination therapy and the ADA monotherapy compared with MTX given alone	Direct and indirect cost, and incremental cost effectiveness ratios. Drug costs will be calculated individually for each patient taking as reference the price published in 2022 by the Health Ministry for the Spanish Health System. Outpatient and inpatient care, other medical cost, home care and productivity loss will be estimated based on the data from eSalud database[68] and from the Minimum Basic Data Set of the Spanish Health Ministry.[69]

ADA, adalimumab; GC, glucocorticoid; MTX, methotrexate.

País Vasco, Castilla y León, Comunidad de Madrid, Castilla La Mancha, Comunidad Valenciana and Comunidad Canaria). In addition, the Instituto de Investigación Biomédica de A Coruña (INIBIC) will carry out the proteomic analysis, and the Instituto de Investigación Sanitaria San Carlos (IdISSC) Musculoskeletal Pathology Group will be responsible for the pharmacogenetic analysis and development of prediction models for drug response.

Recruitment

It will extend over 18 months. The participating study sites attends several 10s of new patients every year, with several hundreds or thousands being followed-up, and many of these sites act as reference centres for other secondary and tertiary hospitals. Candidate subjects will be identified from patients lists AND/OR research databases AND among the new patients attended at the sites.

Subject will not receive any financial compensation for participating in the study.

To ensure subject's retention during follow-up, we will request contact details, carry out reminder phone calls/send emails, review barriers to attend appointments, and educate them in the significance of research follow-up even if they decide to discontinue the study drugs.

Intervention

All subjects entering the study will be centrally randomised at the baseline visit into one of three study arms, in a 1:1:1 ratio:

Arm 1 will receive at the baseline visit ADA 80 mg SC loading dose followed a week later by 40 mg every-other-week starting at week 1. They will also receive MTX oral at the baseline visit, with initial dose of 15 mg/week, increasing up to 25 mg/week.

Arm 2: MTX with the same schedule as in arm 1.

Arm 3: ADA with the same schedule as in arm 1.

In addition to the study drugs, topical adjunctive eye medication will be allowed according to standard practice (intraocular pressure-lowering medication, cycloplegic agents, artificial tears, topical non-steroidal anti-inflammatory drugs…). The use of any biologic therapies with a potential therapeutic impact in NIUs, live vaccines, any other ISD besides the study drugs, intraocular GCs implants or intraocular surgery will be prohibited for the duration of the trial.

Table 2 Study participant inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Adult subjects (≥18 years old)	Subjects with ocular histoplasmosis syndrome, or ocular masquerade syndromes
Diagnosed with non-infectious intermediate, posterior or panuveitis in at least one eye	Evidence or history of malignancy
Who have active disease within the previous 180 days before baseline, and either	Corneal, lens or vitreous opacities precluding the visualisation of the fundus
A documented failure to systemic or local GCs in the previous 6 months, OR	Uncontrolled intraocular pressure
A chronic disease necessitating GC-sparing immunosuppressive treatment (such as multifocal choroiditis with panuveitis, serpiginous choroidopathy, birdshot retinochoroidopathy, diffuse retinal vasculitis, Vogt-Koyanagi-Harada with bullous serous retinal and/or choroidal detachments or sympathetic ophthalmia)	Best-corrected visual acuity (CVA) <20/400
Able and willing to self-administer subcutaneous (SC) injections or have a qualified person available to administer SC injections	History, symptoms and/or MRI findings suggestive of a demyelinating disease
A negative PPD test (or equivalent) and a chest X-ray (CXR) at Screening OR if positive PPD test (or equivalent) and/or a CXR consistent with prior tuberculosis (TB) exposure, the subject must initiate, be currently receiving or have documented completion of a course of TB prophylaxis therapy, according to clinical practice	History of moderate to severe congestive heart failure (NYHA class III or IV)
	Behçet's disease or suspected of Behçet's disease
	Previous exposure to TNFi therapies
	Previous exposure to synthetic ISDs in the previous 6 months before baseline
	Prior intolerability, safety issues or ineffectiveness of MTX and/or ADA
	Use of GCs implants (Iluvien within 3 years, Ozurdex within 6 months before baseline)
	Use of intraocular or periocular GCs injection within 90 days before baseline
	Ocular surgery within 30 days before baseline
	Planned (elective) eye surgery in the following 52 weeks from baseline
	Proliferative or severe non-proliferative diabetic retinopathy
	Neovascular/wet age-related macular degeneration
	Chronic structural damage considered by the Investigator to interfere with measurement of macular thickness, impede the potential for its normalisation or can cause damage independent of the inflammatory process
	Systemic inflammatory disease considered by the Investigator as likely to require high GCs dosage or prohibited medications
	Presence of chronic recurring infections (HBV, syphilis), active TB and/or a history of invasive infection
	Positive pregnancy test
	Breast-feeding or considering becoming pregnant during the study

ADA, adalimumab; GC, glucocorticoids; ISDs, immunosuppressive drugs; MTX, methotrexate.

To ensure a balance of patients across treatment groups and uveitis anatomic locations, patients will be stratified according to the main site of ocular inflammation (intermediate, OR posterior/panuveitis). Randomisation will not be stratified by site due to the small-expected number of subjects per site.

Block randomisation will ensure that an equal number of patients are randomised to each study arm.

The allocation sequence will consist of a computer-generated random number list generated and held in the Clinical Research Unit of Hospital Clínico San Carlos, hidden from participating Investigators. The allocation sequence will be computer-generated, and it will be implemented through the electronic case report form (eCRF; REDCap), which will assign the treatment group. Study data will be collected and managed using REDCap electronic data capture tools hosted at The Health Research Institute of the Hospital Clínico San Carlos.[62 63] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data

Table 3 Study activities

Activity	Screening	Baseline	w1	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	FET	Relapse	Unsch.	70-day follow-up
Informed consent	X																		
Inclusion/exclusion criteria	X	X																	
Medical/surgical history	X	X																	
History of tobacco and alcohol use	X	X																	
Uveitis history	X	X																	
Vital signs/weight/height	X	X														X	(X)		
Physical exam	X	X														X	(X)		
Symptom directed physical exam			X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Chest X-ray	X															X*			
Cerebral MRI†	(X)																		
TB screening	X																		
Serum pregnancy test††	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hepatitis B/C screening	X																		
Syphilis testing (FTA)	X																		
Randomisation		X																	
Best-corrected visual acuity testing	(X)‡	(X)‡		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Tonometry	(X)‡	(X)‡		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Slit lamp exam	(X)‡	(X)‡		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dilated indirect ophthalmoscopy	(X)‡	(X)‡		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Fundus photography	(X)‡	(X)‡					X									X	X		
Optical coherence tomography	(X)‡	(X)‡		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
EuroQol-5D	(X)‡	(X)‡		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Visual Functioning Questionnaire-25	(X)‡	(X)‡					X									X	X		
Hospital Anxiety and Depression Scale	(X)‡	(X)‡					X									X	X		

Continued

Table 3 Continued

Activity	Screening	Baseline	w1	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	FET	Relapse	Unsch.	70-day follow-up
Haematology/ chemistry	X	(X)§	X	X	X	X	X		X		X		X		X	X	(X)		
Monitor adverse events		(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of patient diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)		
Perform drug accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)		
Assessment of direct and indirect costs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)		
Dispense study drugs		X	X	X	X	X	X	X	X	X	X	X	X	X	X		(X)		
Proteomic blood sample	(X)¶	(X)¶					X									X	X		
Pharmacogenetic blood sample	(X)¶	(X)¶																	
Adalimumab levels and antiadalimumab antibodies	(X)¶	(X)¶					X**			X**						X**	X**		

*Chest X-ray will be performed at the 52 weeks/early termination visit in case the patient had a positive TB test at baseline.
†Cerebral MRI will be performed only in those subjects with intermediate uveitis or signs of intermediate uveitis.
‡Values from the baseline visit or from a screening visit up to 14 days before the baseline visit will be used as the values from the baseline visit.
§Total blood count, renal and liver function test from up to 4 weeks before the baseline visit will the required before entering the study.
¶Blood sample will be drawn after signature of the informed consent, as soon as possible, ideally before start of oral GCs.
**Blood samples for the antiadalimumab antibodies will be drawn the week before visits 16, 28, 52. Early termination and relapse visits, up to 24 hours before the patient is scheduled to receive the ADA dosage, and always before the medication is taken.
††Only in women in childbearing
FET, final (w52)/early termination visit; ISD, Immunosuppressive Drug; NYHA, New York Heart Association; PPD, Purified protein derivative ; TNF, Tumor Necrosis Factor; Unsch, unscheduled visit; w, week.

Table 4 Planned methods of statistical analysis for efficacy-related secondary outcomes

Outcome variable	Statistical analysis
Complete abrogation of the ocular inflammatory signs, which is achieved within the first 16 weeks of the study, no treatment failure due to safety or intolerability; compliance with the initial (up to week 16) oral GCs tapering protocol and completion of all study visits from baseline to 16 weeks	MHT, stratified by NIU location. If p-value<0.05, pairwise comparisons using MHT stratified by NIU location will be carried out with Bonferroni adjustment of the pairwise p-values
EQ5D	GEE models nested by patient[70 71] and adjusted by study visit (continuous) and treatment arm (discrete) will be carried out, using a Gaussian family and Identity as link function. Different covariable structures will be tested (independent and exchangeable) and compared using the Bayesian Information Criteria. Time x study arm interactions will assess different effects of time in the evolution of the outcome by arm. P-value<0.05 will be considered as a significant interaction
Visual Functioning Questionnaire-25 Hospital Anxiety and Depression Scale	Changes between Baseline and w16, and the FET visit will be compared between treatment groups using ANOVA
Active chorioretinal lesions; active retinal vascular lesions; macular oedema; ACC; vitreous haze and loss of CVA secondary to inflammation at baseline, week 16, week 52 and relapse visit	MHT, stratified by NIU location. If p-value<0.05, pairwise comparisons using MHT stratified by NIU location will be carried out with Bonferroni adjustment of the pairwise p-values
The time to inflammatory relapse between groups, defined as the time from visit 16 weeks until end of the study, loss of follow-up or appearance of at least one ocular inflammatory manifestation, in those individuals achieving a Good Clinical Response by visit 16 week	Time to relapse between arms will be analysed using log-rank test at a two-sided significance level of 5%. Dropouts due to reasons other than inability to maintain a Good Clinical Response will be considered as censored observations at the time of dropping out. Only subjects able to achieve a Good Clinical Response by visit week 16 will be analysed. We will consider both the time until the onset of the first inflammatory manifestation, each inflammatory manifestation, the first inflammatory manifestation that does not resolve in the following 4 weeks and each inflammatory manifestation that does not resolve in the following 4 weeks.
Best-corrected visual acuity during follow-up	GEE models
Assessment of anti-ADA antibodies (AAA) at weeks 15, 27, 51 and relapse	MHT, stratified by NIU location. If p-value<0.05, pairwise comparisons using MHT stratified by NIU location will be carried out with Bonferroni adjustment of the pairwise p-values
Direct and indirect cost, and incremental cost effectiveness ratios	Cost utility and cost-effectiveness analysis from the perspectives of the National Health System and the Society will be performed. EQ5D scores will derive utility values representing health related quality of life. QALYs will be calculated by the area under the curve assuming a linear evolution of EQ5D values between visits. The average number of QALYs per patient will be calculated for each study arms. Effectiveness will be defined using our primary efficacy outcome. An average cost per patient will be calculated for each study arm, including direct (drug cost, outpatient and inpatient care and other medical cost) and indirect cost (home care, productivity loss): Incremental cost-effectiveness ratios will be calculated, using the MTX monotherapy arm as comparison

ACC, Anterior Chamber Cells; ADA, adalimumab; ANOVA, analysis of variance; CVA, corrected visual activity; EQ5D, EuroQuol 5D-5L; FET, final (w52)/early termination visit; GCs, glucocorticoids; GEE, generalised estimating equations; MHT, Mantel-Haetzel; MTX, methotrexate; NIU, non-infectious uveitis; QALYs, quality-adjusted life years.

manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages and (4) procedures for data integration and interoperability with external sources. After obtaining the informed consent for enrolment and confirming that all eligibility requirements have been met, the Unmasked Investigator (see next section) will log into the eCRF and perform the randomisation. Unmasked investigators will then give their assigned treatment to the subjects.

Authorised rescue medication

During whole study up to two inflammatory relapses (unilateral or bilateral) will be allowed, one during the first period (baseline–week 16: ACC relapse) and one during the second period (week 16–week 52: any location), before declaring the lack of response to the assigned medication. Based on the location and severity of the relapse, a protocolised rescue treatment with Topical AND/OR Local OR Oral GCs will be allowed. In case inflammation cannot be suppressed in 4 weeks, or a new relapse takes place after 4 weeks, it will be declared treatment failure and the subject will exit the study.

Masking

For the duration of the trial, both the study subject and the Unmasked Investigators will be aware of the treatment

Table 5 Trial registration data and protocol summary

Data category	Information
Primary registry and trial identifying number	EudraCT: 2020-000130-18
Date of registration in primary registry	9 March 2021
Secondary identifying numbers	ClinicalTrials.gov: NCT04798755
Source of monetary or material support	Instituto de Salud Carlos III
Primary sponsor	Fundación para la Investigación Biomédica del Hospital Clínico San Carlos
Contact for queries	Luis Rodriguez-Rodriguez, MD (lrrodriguez@salud.madrid.org)
Public title	Combination THerapy with mEthotrexate and adalImumAb for uveitis (CoTHEIA)
Scientific title	Efficacy, safety and cost-effectiveness of methotrexate, adalimumab or their combination in non-infectious non-anterior uveitis: a multicentre, randomised, parallel three arms, active-controlled, phase III open label with blinded outcome assessment study
Countries of recruitment	Spain
Health condition or problem studied	Non-infectious non anterior uveitis
Intervention(s)	Intervention 1: Adalimumab 40 mg every-other-week (plus a 80 mg SC loading dose)+methotrexate oral, up to 25 mg/week, both for a duration of 52 weeks Intervention 2: Methotrexate with the same schedule as in intervention 1 Intervention 3: Adalimumab with the same schedule as in intervention 1
Key inclusion and exclusion criteria	Age≥18 years old Diagnosed with non-infectious intermediate, posterior or panuveitis in at least one eye Active ocular disease Lack of satisfactory response to systemic and/or local glucocorticoid (GC) therapy AND/OR diagnoses of a chronic disease usually necessitating GC-sparing immunosuppressive treatment
Study type	Phase III, multicentre,prospective, randomised, single-blinded with masked outcome assessment, parallel three arms with 1:1:1 allocation, active-controlled, superiority study design
Date of first enrolment	N/A
Target sample size	64 per treatment arm (192 in total)
Recruitment status	Not yet recruiting
Primary outcome	Complete resolution of the ocular inflammatory signs, which is achieved within the first 16 weeks of the study, and maintained during follow-up until the end of the study (week 52)
Key secondary outcomes	Safety, cost-effectiveness

N/A, not applicable.

assigned. Considering the differences between study drugs (MTX and ADA) regarding appearance, route of administration and schedule, in order to make them unaware of the medication prescribed, the use of placebo would be necessary. However, taking into account that both drugs have been proven effective in the treatment of NIU, the duration of the trial (up to 52 weeks), and the need for biweekly subcutaneous (SC) injections of one of the drugs (ADA), we consider unethical for the subject the use of placebo in the present trial.

Besides the Unmasked Investigators, the rest of participating investigators will be considered Masked Investigators (ophthalmologists performing the clinical eye exams, visual acuity examiners, Optical Coherence Tomography (OCT) operators, fundus photographers, fundus graders and administrators of subject's questionnaires) and will not be aware of the treatment assigned to prevent bias in study outcomes.

Several steps will be taken to avoid the Masked Investigators discovering the subject assignment: they will have no part in handling or prescribing medication; subjects will be given dark bags to place and keep their medication in throughout the trial and study visits to minimise the chances of the Masked Investigators seeing the medications. Additionally, subjects will meet with the Unmasked Investigator first, before seeing any Masked Investigators, keeping any study medication in his/her office for the entire patient visit; reviewing the appearance of any AE with the subjects before seeing any Masked Investigators, and reminding the subjects not to discuss their dosing and mediation name with the Masked Investigators.

Study procedures

Study visits will be the baseline visit, visits at weeks 1, 4, and every 4 weeks thereafter until (a) the subject is determined as unable to achieve complete resolution of the ocular inflammatory process by week 16, OR; (b) the subject is determined as unable to maintain a complete resolution of the ocular inflammatory process, between weeks 16 and 52 OR; (c) the subject completes 52 weeks of this clinical trial, OR; (d) the study is stopped due to the findings of the Data Security Monitoring Board, OR and (e) the subject meets any of the study finalisation criteria.

Informed consent has to be acquired before carrying out any study procedure, including screening tests (online supplemental file 1 contains a sample informed consent). Before baseline (when the subject is randomised), several screening visits can take place up to 14 days before that visit, in order to obtain all the required complementary tests to assess eligibility. The visit window for all scheduled visits is ±3 days through week 4 and ±7 days for all visits following the week 4 study visit. Table 3 provides an overview of the study activities.

After the trial, all patients will return to standard care and will be able to continue with their assigned study medication.

Data management and monitoring

An Unmasked Investigator in each centre will review and crosscheck for consistency and completeness all data collected in RedCap within 24 hours of the study visit. If the forms are not filled out completely, the responsible person will be contacted for providing the missing data. An external monitoring service will conduct regular checks of the data regarding errors and inconsistencies, supervising data collection, management and quality control, and will submit queries to the site investigators.

Safety

Non-serious AEs will be defined as an unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of the study medication or procedure, whether or not considered related to the study medication. Both MTX and ADA may be temporarily suspended in case of non-serious AEs, such as laboratory alterations, infections, and intolerance. In addition, MTX dosage may also be reduced in case of laboratory alterations and/or intolerance. Dose reductions and temporary discontinuations will be decided by the Masked Investigator, who must remain unaware of the medication and dosage assigned to the subject, so preconceptions regarding the study drugs do not interfere with their management. The Masked Investigator will issue three recommendations; one for each medication arm the subject may be included. Then, the Unmasked Investigator will implement the recommendation according to the arm the subject is included.

SAEs will be defined as any AE that results in death, is life threatening, requires hospitalisation, or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

All AEs will be recorded in clinical records and a medically qualified investigator will assess the relationship of SAEs to the study medications.

All SAE that occurs during the trial must be reported immediately by mail or fax to the Pharmacovigilance Unit within 24 hours of its occurrence. The investigator will complete and sign the SAE notification form to be sent by e-mail.

The Pharmacovigilance Unit will review the form received and, if applicable, ask for additional information to the investigator. The investigator should provide the requested information or any new information regarding the case, especially if the initial assessment in severity or causality has been changed, following the procedure previously described.

The Pharmacovigilance Unit is responsible for submitting as soon as possible all Suspected Unexpected Serious Adverse Reactions (SUSARs) collected during the study to the Spanish Health Authorities and Ethic Committee, according with the Spanish legislation: no later than 15 calendar days (seven in case of fatal or life-threatening cases) after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

Data and Safety Monitoring Committee

Only after the Data and Safety Monitoring Committee (DSMC) reviews and approves the protocol will patients be enrolled. In addition, the group will meet regularly throughout the study and review information on data quality, enrolment, patient retention and study outcomes according to DSMC charter. The DSMC will be independent from the Sponsor, Funding Body and Principal Investigator and will include experts in the fields of ophthalmology, rheumatology and epidemiology.

Adherence

Adherence will be monitored using a Patient's Diary (where they will register all study medication administered outside of the study visit (ie, at home), including reasons for missing dosages) and by verifying the returned empty medication (partially/completely empty blisters of study medication, AND/OR cartons and sharps containers for MTX, ADA and oral GCs).

Patient and public involvement

No patient involved.

Statistical analysis plan

The intention to treat (ITT) set will include all subjects who were randomised.

The safety set will consist of all subjects who received at least one dose of study medications. Per protocol analysis will also carry out. Missing data will be imputed using multiple imputation-chained equations.

Sample size determination

ADA arm: after 1 year (50 weeks) of treatment, 20.3% of NIU patients achieved an outcome similar to our *primary efficacy outcome*.[28]

MTX arm: after 6 months of treatment, 65% of NIU patients achieve also similar outcome;[64] we estimate that of those patients, 18%[65] and 16%[66] will be unable to maintain our outcome due to AEs and inefficacy, respectively; therefore, at 1 year, 43% will achieve our *primary efficacy outcome*. This figure will be assumed as the percentage of subjects treated with monotherapy achieving the primary efficacy outcome.

MTX+ADA arm: we will assume that combination therapy will increase the percentage of subjects achieving our *primary efficacy outcome* by 23% compared with the monotherapy arms.

To detect statistically significant differences between groups with a power of 80% and a significance level of 0.05, it will be necessary to recruit 54 patients per study arm (162 in total). Since the follow-up period is 52 weeks, losses of 15% will be assumed, increasing the sample size to 64 patients per study arm (192 patients in total). In order to test the difference between the treatments, superiority or relevant clinical improvement has been considered from a delta of 5% of the effect.

Planned methods of statistical analysis for efficacy-related objectives

The primary analysis will be a Mantel–Haenszel test (MHT), stratified by NIU location, comparing the combination therapy arm and the single ISDs arms (both arms combined), and performed in the ITT set. Achievement of the Good Clinical response will be considered the binary response variable: those subjects achieving a Good Clinical versus those not achieving the outcome (regardless the cause). The exposure variables will be the treatment arm: those subjects receiving combination therapy versus those receiving either monotherapy. Uveitis location will be the strata: intermediate uveitis versus posterior OR panuveitis. If the results of the primary analysis are significant, then pairwise comparisons using MHT stratified by NIU location will be carried out. P values of the pairwise comparisons will be adjusted using the Bonferroni method. No interim efficacy-related analysis will be carried out.

Secondary efficacy-related analyses are designed to test the hypothesis that treatment assignment affects a given outcome, after controlling for selected covariates. Details can be found at table 4.

Planned methods of statistical analysis for safety-related aims

The safety analysis will be performed in the safety set. Treatment-emergent AEs (events with an onset date on or after the first study drug administration until 70 days following the last study drug administration) will be summarised by treatment group using descriptive statistics. SAEs with onset after informed consent but before the first study drug administration will be considered as pretreatment SAEs and reported separately.

AEs will be tabulated by system organ class and preferred term whereby the most current implemented MedDRA dictionary will be used. In addition, summaries by severity and relationship to study drug will be done. Certain AEs, such as serious or severe, leading to premature withdrawal, will be listed and described in detail. AEs of special interest for treatments will be defined in the statistical analysis plan and analysed separately. In addition to the descriptive statistics provided, Fisher's exact test will be used for comparisons between treatment groups.

Genetic analysis

SNPs genotypes will be determined by real-time PCR amplification using Taqman probes and following standard procedures. Duplicate genotypes of 10% of the samples, concordance (all p>0.05) with the Hardy–Weinberg equilibrium and with SNP frequencies in the HapMap European collection will be used for quality control.

Comparison of the proportion of subjects achieving the primary efficacy outcome between genotypes will be carried out using a χ^2 test or Fisher's exact test, when required. Dominant, recessive and additive models of effects will be considered for each SNP. P values will be adjusted using the Bonferroni method. Each study arm will be analysed separately.

Proteomic analyses

Discovery phase: Shotgun proteomic analysis[56–58] will be performed on serum samples from a representative group of subjects from each study arm with extreme responses (n=20): those achieving the *primary efficacy outcome* and those not being able to achieve a good clinical response by week 16.

Verification phase: targeted proteomics will be used for verification of protein markers with predictive potential in a randomly selected larger samples set (n=80). After MRM tests, relative quantification methods of the proteins will be designed.[59]

Validation phase: best candidates from the previous phase will be validated using absolute quantification tests (antibody-based microarrays) in the whole set of subjects.[60 61]

Patient subgroup identification

Based on baseline visits patient's characteristics (demographic, disease and clinical-related variables), those genotypes significantly associated with the primary efficacy outcome, and the previously identified serum proteins in the verification phase, prediction models for MTX, ADA and Combination therapy response will be developed using a machine learning method (Random Forests[67]). Models' performance will be assessed with the area under the receiver operating characteristic curve, and calibration curves. Models using only clinical data, only biomarkers data and the combination of both will be developed, to assess the contribution of biomarkers to the models' predictive ability. Due to the modest sample size we plan to recruit, we will not divide our sample in training, validation and test data sets. All subjects will be considered as part of the training data set, and a 10-fold cross-validation will be carried out to internally validate our models.

ETHICS AND DISSEMINATION

The protocol (version 2, 11 September 2020), annexes and informed consent forms have been approved by the Clinical Research Ethic Committee (CREC) at the Hospital Clínico San Carlos (Madrid, Spain) and the Spanish Agency for Medicines and Health Products (AEMPS). The local approvals corresponding to the participating centres will be obtained and documented before starting the study in that centre as per centre requirements. The promoter will be the CREC interlocutor corresponding to his/her centre in everything related to the present study. It will keep CREC informed of the evolution of the study in the centre and of the possible minor incidents and modifications that may occur. Any relevant modification to the protocol must receive express approval from the reference CREC and the AEMPS before its implementation, unless there are risk circumstances for the participating subjects, in which case the precise measures to

ensure the integrity of the study subjects will be implemented immediately, pending the corresponding approvals. The trial is registered at clinicaltrialsregister.eu (EudraCT:2020-000130-18) and clinicaltrials.gov (NCT04798755). This study involves human participants and was approved by Hospital Clínico San Carlos Ethics Committee, approval ID '20/510–EC_M'. Participants gave informed consent to participate in the study before taking part.

No study related activities will be carried out before obtaining a written informed consent from the patient. The investigator will be responsible for: (a) providing each patient with an information sheet about the trial and the objectives, methods, foreseeable benefits and potential risks of the study, (b) discussing the information with the patient, in terms understandable for the subject and (c) explaining to patients that they are totally free to refuse their participation in the study or to abandon it at any time and for any reason. If the subject agrees to participate in the Biobank Substudy, a second independent informed consent will be collected, which will include the possibility of storing the samples not used in the present study in the Collection of Samples for Research in Rheumatic Diseases of the Rheumatology Department of the Hospital Clinico San Carlos (and, in a second phase, when the Coordinating Investigator of this study deems it appropriate and always in the event that the samples has not been used up, the remainder will be stored in the Hospital Clinico San Carlos Biobank).

All the data will be treated confidentially at any times: data will be pseudonimised, the paper forms will be kept in locked cabinets, the eCRF is located in a secure server and the person in charge of the analysis will not be able to access identification data of the subjects.

Table 5 summarises the study protocol and trial registration information.

Data obtained through this study may be provided to qualified researchers with academic interest in uveitis. Data or samples shared will be coded, and donated to a Registered Biobank and made available under legal requirement. Approval of the request and execution of all applicable agreements are prerequisites to the sharing of data with the requesting party.

Regarding dissemination, in order to communicate the clinical trial progress and findings to a broad group of stakeholders, we will elaborate a dissemination plan which will include production of materials adapted to scientific meetings, scientific publications, patients and other stakeholders. A summary of the final version of the study protocol will be made available through the Spanish Clinical Trial Registry and Clinicaltrials.gov database. The promoter will be the only with access to the participant-level data, following the regulation on data protection.

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Contributors L-RR, AL-P, EC and DD-V conceived of the study. L-RR, AL-P, EP, DD-V, MC-C, AF, AG-A, JG-G, SM, ABR and LAT initiated the study design and helped with implementation. L-RR is the funding holder. AL-P and ABR provided statistical expertise in clinical trial design. VC provided expertise regarding the proteomic analysis design. L-RR provided expertise regarding the pharmacogenetic analysis. AL-P, ABR and L-RR will conduct the primary statistical analysis. ABR, AL-P, VC, EC, LC, MC-C, AF, FMFH, AG-A, JG-G, JJM, LL-O, LM-C, SM, DP, JAP, BR-L, EP, DD-V, EM, LAT and L-RR contributed to refinement of the study protocol and approved the final manuscript.

Funding This work was supported by the Instituto de Salud Carlos III, grant number [ICI19/00020]. Sponsor: Fundación para la Investigacion Biomédica del Hospital Clínico San Carlos. Executive Committee: Administrative and executive arm of the clinical trial, providing overall oversight for the study and making decisions on day-to-day operational issues (Study Coordinator (Luis Rodriguez-Rodriguez), a representative from the Spanish Clinical Trial Network (Amanda López Picado), and 5 Site Directors (these seats will be rotatory, with changes every 6 months months)); Data Coordinating and Analysis Committee: Supervising data collection,management and quality control, designing the statistical analysis plan, performing unmasked data analysis and preparing interim and final reports for the Data Security Monitoring Board and the Executy Committee (Study Coordinator (Luis Rodriguez-Rodriguez), a representative from the Spanish Clinical Trial Network (Amanda López Picado) and Ester Carreño); Biobank and Biomarker Identification Committee (Maintaining an up-to-date manual of operations for blood extraction, processing and storage, and monitoring procedures adherence, supervising biological sample collection, sample shipment coordination, coordinating the phamacogenetic and proteomic analysis (Study Coordinator (Luis Rodriguez-Rodriguez), a representative from the Instituto de Salud Carlos III Biobank Platform (Elena Molino), a representative the Instituto de Investigación Biomédica de A Coruña, a representative from, the Data Coordinating and Analysis Committee); Data Security Monitoring Committee (PierGiogio Neri, Andrew Dick, Loreto Carmona).

Disclaimer The study sponsor had no role in the study design; collection, management, analysis and interpretation of data; writing of the report and the decision to submit the report for publication.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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HOJA DE INFORMACIÓN AL PACIENTE

Solicitamos su participación en un proyecto de investigación promovido por investigadores de su centro y dirigido por el doctor Luis Rodriguez del Hospital Clínico San Carlos (Madrid). El estudio se titula **"Eficacia, seguridad y coste-efectividad del metotrexato, adalimumab, o su combinación en uveítis no anterior no infecciosa: un estudio multicéntrico, aleatorizado, paralelo de 3 brazos, con control activo, de fase 3, abierto, con evaluador cegado: Co-THEIA (CombinationTHerapy with mEthotrexate and adalImumAb for uveitis)"**

Siguiendo los estándares internacionalmente reconocidos y la normativa legal vigente en España sobre investigación, este ensayo clínico cumple todas las exigencias legales y ha sido aprobado por el Comité Ético de Investigación con medicamentos del Hospital Clínico San Carlos así como por la Agencia Española de Medicamentos y Productos Sanitarios.

Sin embargo, antes de aceptar participar o no, es importante que lea detenidamente la siguiente información y que realice todas las preguntas y aclare todas las cuestiones que crea conveniente con un familiar/amigo o con su médico.

¿Tengo que participar?

La participación en el estudio es completamente voluntaria. Rechazarla no acarreará ningún deterioro en la calidad de la asistencia ni en su atención médica. Además, podrá retirarse en cualquier momento del estudio sin tener que dar explicaciones y sin que ello repercuta en los

cuidados médicos que reciba. Su médico también podrá decidir, por alguna consideración médica o por cualquier otra razón, retirarle del estudio si así lo cree conveniente.

Así mismo, el hecho de que usted participe en este estudio no altera de ninguna manera ni sus tratamientos habituales ni el seguimiento de las enfermedades que tenga (en caso de que las tuviera).

¿En qué consiste el estudio y cómo se va a llevar a cabo?

Su médico le ha diagnosticado una uveítis no infecciosa, una inflamación de una parte del ojo que no está causada por un microorganismo (bacteria, hongo o virus).

Para tratar esta inflamación es posible que su oftalmólogo y/o reumatólogo/inmunólogo/especialista en Medicina Interna ya le haya pautado distintos tratamientos, principalmente corticoides. Sin embargo, estos fármacos a veces no son suficientes para controlar enfermedad. Por otro lado, es posible que haya sido diagnosticado/a de algún tipo de uveitis que se asocie a una inflamación más persistente. En ambos casos, en la actualidad disponemos de distintos medicamentos para el tratamiento pero solo tiene indicación aprobada el adalimumab. En este estudio vamos a comparar este medicamento y el metotrexato, solos o combinados.

El metotrexato es un fármaco que inhibe el sistema inmunitario y esto permite reducir la inflación del ojo. Se lleva utilizando desde hace más de 50 años en el tratamiento de otras enfermedades inflamatorias crónicas y más reccientemente (más de 30 años) en el tratamiento de las uveitis. Se puede tomar en pastillas o inyectado en la piel (vía subcutánea), su médico según su caso le indicara como y cuando tomarlo.

El adalimumab es otro medicamente que también inhibe el sistema inmunitario y reduce la inflamación, pero utiliza otro mecanismo de acción. Se lleva utilizando en el tratamiento de las uveitis desde hace más de 10 años, administrándose por vía subcutánea.

Si usted decide participar en el estudio podrá ser asignado a uno de los tres grupos en estudio: metotrexato, adalimumab y ambos (metotrexato+adalimumab). La asignación será al azar, es decir ni usted ni su médico decidirá que tratamiento recibe. Indistintamente el grupo al que sea asignado, las visitas y las pruebas que se le realicen serán las que habitualmente se realizan a pacientes como usted. Además, en el caso de que haya sido diagnosticado de algunos subtipos de uveítis (como es la uveítis intermedia), se le realizará una resonancia magnética cerebral con gadolinio antes de iniciar el estudio. Esto es debido a que estos subtipos de uveitis podrían estar asociados a la presencia de enfermedades desmielinizantes del sistema nervioso central, en las que el uso de adalimumab se encuentra contraindicado.

Usted tendrá acudir cada 4 semanas al centro. En estas visitas su médico se encargará revisar la situación del ojo (examen del ojo, agudeza visual…), los eventos adversos y la adherencia al

tratamiento. Además, deberá completar algunos cuestionarios para evaluar su calidad de vida, los costes y los fármacos que toma (aproximadamente 15 minutos). Para completar estos cuestionarios dispondrá de ayuda del personal del centro.

Adicionalmente le solicitaremos permiso para la extracción de unas muestras de sangre al inicio, tras 16 semanas, cuando finalice y en el caso de que tuviera algún brote de la uveítis durante el estudio. Estas muestras serán utilizadas para hacer análisis genéticos y de proteómica para identificar marcadores que permitan conocer más su enfermedad y /o que puedan estar asociados a una mejor respuesta al tratamiento. También, en el caso de que fuera a recibir adalimumab, para medir los niveles en sangre de ese fármaco. Por último, con el objetivo de llevar a cabo futuros estudios que nos ayuden a conocer mejor la enfermedad que usted padece, parte de estas muestras serán depositadas y almacenadas en el Biobanco vinculado a su centro en régimen de Biobanco (por ello, en el caso de acceder a que podamos extraer estas muestras, durante el proceso asistencial, se le facilitará para su revisión y firma una copia del consentimiento informado del Biobanco vinculado a su centro). Un Biobanco es un establecimiento de almacenamiento de muestras de origen humano bajo criterios de calidad, orden y destino para su utilización en investigaciones nacionales o internacionales dentro del campo de la biomedicina. Su funcionamiento se centra en gestionar, bajo criterios de seguridad, calidad y eficiencia; la recepción, procesamiento, almacenamiento y posterior cesión de muestras a los investigadores solicitantes, para que utilicen las mismas en sus proyectos de investigación; siempre y cuando, éstos cumplan todos los requisitos éticos y legales vigentes, tal y como establece el Real Decreto 1716/2011 de 18 de noviembre, la Ley de Investigación Biomédica 14/2007, (LIBM) y la normativa que la complementa. Una vez depositadas las muestras en el Biobanco, estas pueden ser cedidas a los investigadores que hayan pasado la

aprobación de un Comité de Ética de Investigación Clínica y del Comité de Ética y del Comité Científico del Biobanco, tal y como se establece en la normativa aplicable (Real Decreto 1716/2011 de 18 de noviembre y la LIBM.

La donación de estas muestras no impedirá que usted o su familia puedan usarlas cuando sea necesario por motivos de salud, siempre que estén disponibles.

¿Puedo restringir el uso que se le de las muestras que me sean extraídas?

Usted puede indicarnos si quiere establecer algún tipo de restricción sobre sus muestras y datos, en relación con su posible uso en determinados proyectos de investigación o en cuanto a determinadas cesiones. Para ello dispone de un apartado específico en la hoja de firma del consentimiento informado.

¿Cómo sabré en que se usan mis muestras?

El Biobanco y/o la persona responsable de la investigación tendrán a disposición de los participantes la información sobre los proyectos de investigación en los que se utilicen las muestras y datos.

En determinadas circunstancias el Comité de Ética competente podrá decidir si es necesario contactar con el participante para facilitarle información de manera individualizada.

De producirse un eventual cierre del Biobanco o revocación de la autorización para su constitución y funcionamiento, la información sobre el destino de las muestras estará a su disposición en el Registro Nacional de Biobancos para Investigación Biomédica del Instituto de

Salud Carlos III (ISC III), con página web www.isciii.es, con el fin de que pueda manifestar su conformidad o disconformidad con el destino previsto para las muestras.

¿Y si obtienen alguna información clínicamente relevante e inesperada como resultado del análisis de mis muestras?

Existe la posibilidad de que las muestras que han sido cedidas al Biobanco sean utilizadas en **estudios de biología celular, molecular y/o genéticos**. En ocasiones, en este tipo de estudios se puede descubrir información no buscada que puede ser relevante para su salud o la de su familia. Si ese fuera el caso, los resultados obtenidos serán validados y analizados por profesionales y por un Comité de Ética para determinar si son fiables en un porcentaje óptimo que aconseje su comunicación a las personas afectadas.

Usted debe saber que tiene derecho a conocer, o no, la información obtenida con el análisis de sus muestras. En el caso de que usted decida no ser informado, la ley establece que cuando la información obtenida sea necesaria para evitar un grave perjuicio para la salud de sus familiares, un Comité de expertos estudiará el caso y deberá decidir entre la conveniencia o no de informar a los afectados o a sus representantes legales.

¿Qué beneficios puedo esperar por el hecho de participar en el estudio?

Puede ocurrir que usted no obtenga ningún beneficio personal de la participación en este proyecto de investigación. En cualquier caso, su participación en este estudio contribuirá al avance del conocimiento sobre el tratamiento de la uveítis no infecciosa.

¿Qué incomodidades o riesgos puede suponer mi participación en el estudio?

Entre los efectos secundarios más habituales del metotrexato están el dolor de cabeza, los moratones y sangrados, el aumento de las infecciones, las náuseas y vómitos, la diarrea, los dolores musculares, el cansancio, la pérdida de cabello y la afectación hepática.

Por su parte, el adalimumab presenta los siguientes efectos secundarios: molestias o dolor en el punto de inyección, erupción cutánea, dolor de cabeza e infecciones (siendo las más habituales las de las vías respiratorias altas (catarros entre otros) y la sinusitis).

En el caso de administrar de manera conjunta ambos fármacos los efectos adversos podrían ser más intensos y aparecer algunos desconocidos. En este momento, la administración de estos dos medicamentos de manera conjunta no está autorizada.

En el caso de que se le tuviese que realizar una resonancia nuclear magnética con gadolinio, el uso de este contraste puede verse asociado a eventos adverso agudos en 1 de cada 1000 individuos, siendo los más frecuentes de la aparición de rash, urticaria y nauseas. Además, ha sido descrita la posibilidad de depósito de esta substancia a nivel cerebral y en otros tejidos, tras administraciones repetidas.

¿Cuáles son mis derechos y cómo van a ser tratados mis datos?

Toda la información que se registrará de usted será estrictamente confidencial. De acuerdo con el Reglamento General de Protección de Datos (RGPD) (Reglamento (EU) 2016/679), además de los derechos de acceso, rectificación, oposición y cancelación de datos (Ley Orgánica 3/2018, de

5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales), también tiene derecho a limitar el tratamiento de datos y solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar sus derechos, diríjase al investigador principal del estudio. No obstante, le recordamos que los datos no se pueden eliminar, aunque deje de participar en el ensayo para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho.

En todo momento se mantendrá el anonimato de los pacientes y, para ello, en ninguno de los documentos del estudio aparecerá su nombre, sino que le será asignado un número que será el que se utilice en todos ellos. En todos los informes escritos y publicaciones, sólo aparecerá su número de referencia. Sólo el médico responsable del estudio guardará, en condiciones de seguridad, la lista que relaciona los nombres de los pacientes con los números de referencia asignados a cada uno.

Sólo tendrán acceso a los datos del estudio el equipo investigador y el monitor del estudio, miembros del comité, autoridades sanitarias competentes y/o de la agencia reguladora (AEMPS) para asegurar que el estudio se está llevando a cabo con las leyes vigentes y la reglamentación sanitaria. Firmando este documento, usted está autorizando este acceso. Además, los resultados del estudio siempre serán presentados de manera global y nunca de forma individualizada.

El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal solo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si usted hubiera otorgado su consentimiento para ello, y si así lo permite la ley y requisitos éticos aplicables.

Si realizáramos transferencia de sus datos codificados fuera de la UE a las entidades de nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren con nosotros, los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las autoridades de protección de datos. Si el participante quiere saber más al respecto, puede contactar al Delegado de Protección de Datos del promotor o Investigador Principal.

¿Mi participación supondrá algún coste o compensación económica?

Su participación en este estudio no supondrá para usted ningún coste económico, así como tampoco será recompensado económicamente por ello. El estudio dispone de una póliza de seguros que se ajusta a la legislación vigente (Real decreto 1090/2015) y que le proporcionará la compensación e indemnización en caso de menoscabo de su salud o de lesiones que pudieran producirse en relación con su participación en el estudio, siempre que no sean consecuencia de la propia enfermedad que se estudia o de la evolución propia de su enfermedad como consecuencia de la ineficacia del tratamiento. Este estudio se considera de Bajo Nivel de

Intervención (estudios de bajo riesgo, muy parecidos a la práctica clínica habitual), por lo que la póliza con la que está usted cubierto es la póliza de Sistema de Salud.

Si usted tiene alguna duda o quiere más información, no dude en consultar con el médico responsable que le está solicitando este consentimiento.

¿Cómo obtener información adicional?

Si desea información adicional sobre el estudio puede contactar con:

_____

GRACIAS POR LEER ESTA INFORMACIÓN

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CONSENTIMIENTO INFORMADO PARA LOS PACIENTES

Título del estudio: **"Eficacia, seguridad y coste-efectividad del metotrexato, adalimumab, o su combinación en uveítis no anterior no infecciosa: un estudio multicéntrico, aleatorizado, paralelo de 3 brazos, con control activo, de fase 3, abierto, con evaluador cegado: Co-THEIA (CombinationTHerapy with mEthotrexate and adalImumAb for uveitis)"**

Yo……..

con DNI/NIF: ……

(Nombre, apellidos y número de identificación del participante, puño y letra del paciente)

DECLARO:

- Que he hablado con ……..

(Nombre del médico, puño y letra del paciente)

- Que he leído la hoja de información que se me ha entregado sobre el estudio.
- He comprendido la información recibida y he podido formular todas las preguntas que he creído oportunas.
- Comprendo que mi participación es voluntaria y que en cualquier momento puedo revocar mi consentimiento sin tener que dar explicaciones y sin que afecte en ningún aspecto a mi relación con el personal médico ni a la atención recibida por su parte.
- He recibido una copia firmada y fechada de este Consentimiento Informado.

Presto libremente mi conformidad a participar en este estudio y doy mi consentimiento para:

La obtención de las muestras indicadas en la Hoja de Información que se me han facilitado y su cesión al Biobanco vinculado a su centro, en las condiciones indicadas, para su utilización en cualquier investigación biomédica	Si	No
Ser informado de los resultados de las investigaciones que sean de interés para mi salud Teléfono de Contacto ……	Si	No
Deseo indicar restricciones al uso de los datos o de las muestras que me sean extraídas …….. …… ……..		

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EN CONSECUENCIA, DOY MI CONSENTIMIENTO PARA FORMAR PARTE DE ESTE PROYECTO DE INVESTIGACION.

Firma del paciente:	Firma del médico responsable:
Nombre y apellidos:	Nombre y apellidos:
……	……
Fecha: ……	Fecha: ……

Rivas AB, *et al. BMJ Open* 2022; 12:e051378. doi: 10.1136/bmjopen-2021-051378