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Clinical science

Efficacy and safety of abatacept to treat active birdshot uveitis: a prospective open label interventional proof-of-concept trial

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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bjo-2022-321585>).

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Received 1 April 2022

Accepted 16 December 2022

Published Online First

30 December 2022



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To cite: Schauwvlieghe PP, Van Calster J, Herbort Jr. CP, et al. *Br J Ophthalmol* 2024;**108**:244–252.

ABSTRACT

Background/aims Birdshot uveitis (BU) is a chronic autoimmune posterior uveitis, mostly affecting middle-aged Caucasians. There is a strong association with HLA-A29 and T-cell activation. Safety and efficacy of abatacept, an inhibitor of T-cell costimulation, is tested in active BU.

Methods Fifteen patients with active BU were treated with monotherapy of weekly subcutaneous injections of abatacept 125 mg/mL. Time-to-treatment failure was evaluated as a primary outcome. The secondary objective was to evaluate the utility of different outcome measures to monitor disease activity. Safety was evaluated by adverse event reporting and serial blood analyses.

Results At the year-1 endpoint, there was significant improvement in vitreous haze grade ($p=0.0014$), central choroidal thickness (CCT) ($p=0.0011$), Fluorescein Angiography (FA) Score ($p=0.0014$), Indocyanine Green Angiography (ICGA) Score ($p<0.001$) and total dual FA-ICGA Score ($p<0.001$). Best corrected visual acuity (BCVA) ($p=0.8354$) and central retinal thickness (CRT) ($p=0.3549$) did not change significantly. There were no serious adverse events reported. In total, 4 out of 15 patients left the trial during year 1 of whom 2 experienced treatment failure.

Conclusions Abatacept is very efficacious to treat both retinal vasculitis and choroiditis in patients with BU and is well tolerated. BCVA and CRT are inadequate to monitor disease activity. On the other hand, CCT is a promising non-invasive tool to detect treatment response in early active BU and dual FA-ICGA Score is very helpful to evaluate retinal vasculitis and choroiditis quantitatively.

Trial registration number NCT03871361.

INTRODUCTION

Birdshot uveitis (BU) or birdshot retinochoroiditis is a chronic bilateral, autoimmune posterior uveitis, with dual and independent retinal and choroidal vasculitis.¹ There is a clear association with HLA-A29^{2,3} and therefore HLA-A29 retinochoroiditis probably is a more accurate name for the disease.⁴ Although the HLA-A29 allele is found in up to 7% of Caucasians,⁵ BU is a rare disease affecting approximately 1–5 persons in 500 000.^{6,7} This supports that the HLA-A29 molecule itself is not sufficient to cause disease and that BU is mediated by additional aetiological triggers.⁸ However, the undisputed involvement of

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Birdshot uveitis (BU) is a T-cell-mediated autoimmune disease.
- ⇒ There is no standardised protocol to monitor BU.

WHAT THIS STUDY ADDS

- ⇒ Abatacept is a very promising drug to treat BU.
- ⇒ Treatment response can be evaluated by central choroidal thickness in the first 6 months of the disease.
- ⇒ Dual Fluorescein Angiography–Indocyanine Green Angiography scoring is an adequate and quantitative monitoring tool.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The role of abatacept can be explored in other diseases with stromal choroiditis.
- ⇒ Vigilant follow-up to detect cancer and more specifically melanoma is important in patients with BU, treated with abatacept.

the major histocompatibility complex (MHC) class I molecule HLA-A29 points towards an important role for the antigen presentation pathway with subsequent T-cell activation.⁹

BU is typically found in middle-aged Caucasians, with slightly more women than men affected.⁷ The disease has an indolent course with mostly mild symptoms in the early stages and preserved visual acuity. Therefore, diagnosis is often delayed. Unfortunately, the disease is chronic, often progressive and has significant potential for irreversible tissue damage and visual loss.⁷ The mainstay of treatment is long-term systemic immunosuppressive treatment. Apart from corticosteroids,^{10,11} various classic immunomodulatory treatments, such as cyclosporine A, tacrolimus, azathioprine, methotrexate and mycophenolate mofetil have been studied.^{11–18} Although the visual function can be stabilised mostly with these drugs, the many adverse events in this middle-aged patient group, make it difficult to tolerate chronic treatment. Treatment with biologicals, such as anti-Tumor Necrosis Factor (TNF)- α drugs, has led to a revolution in treatment

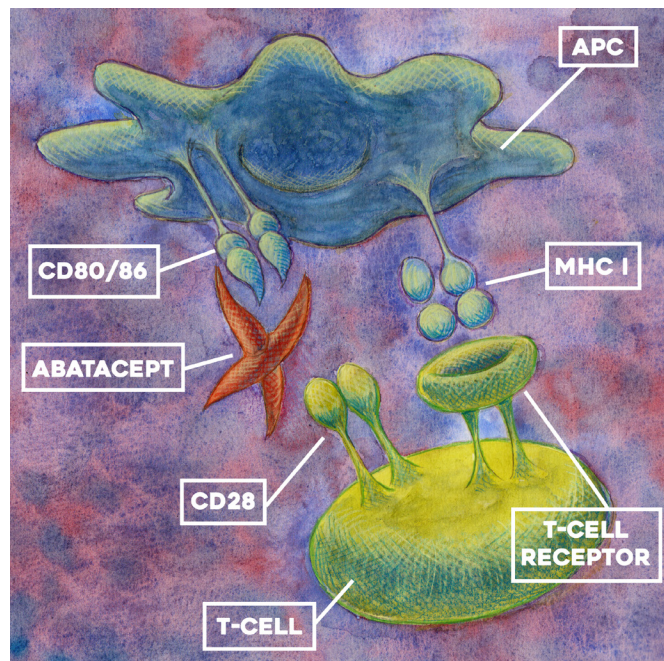


Figure 1 An antigen, presented by the major histocompatibility complex (MHC) I complex (such as HLA-A29) on the surface of the antigen presenting cell (APC) binds with the T-cell receptor. Stimulation of the T cell requires a costimulatory binding between CD80/86 on the surface of the APC and CD28 on the surface of the T-cell receptor. Abatacept binds CD80/86 and inhibits the costimulatory binding. Therefore, the T cell can not be activated. Courtesy of Ivo De Wispelaere.

of non-infectious posterior uveitis (NIPU), with proven efficacy and better tolerability, although failure during adalimumab therapy still is as high as 30% in NIPU.¹⁹ In BU, numerous biological treatments have been described in small studies.^{20–25} In the post hoc analysis of the VISUAL I trial (Efficacy and Safety of Adalimumab in Patients With Active Uveitis), there was a favourable numerical trend with a lower risk of treatment failure with adalimumab compared with placebo in 44 patients with active BU, although this was not statistically significant ($p=0.089$).²⁶ More specifically, adalimumab seems to be more effective to treat retinal vasculitis and macular oedema, but less effective to treat choroiditis.²⁷

In BU, a processed peptide of unknown origin is presented on the MHC class I HLA-A29 molecule to activate cytotoxic CD8+ T cells, leading to a complex autoimmune cascade. Abatacept is a fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4. In order for a T cell to be activated and produce an immune response, an antigen-presenting cell must present two signals to the T cell. One of those signals is the MHC, combined with the antigen, and the other signal is the CD80 or CD86 molecule (also known as B7-1 and B7-2). Abatacept binds to the CD80 and CD86 molecule and prevents the second signal. Without the second signal, the T cell cannot be activated (figure 1). Therefore, abatacept seems to be an interesting candidate drug to treat MHC-1-opathies, and BU in particular. Abatacept is widely used in rheumatology. In rheumatoid arthritis (RA) for instance, abatacept has similar efficacy and a slightly better safety profile, compared with adalimumab.²⁸ In uveitis, abatacept is used to treat juvenile idiopathic arthritis-associated uveitis,^{29–33} but there is no experience with posterior uveitis.

To evaluate the efficacy and safety of abatacept in BU, we conducted a 2-centre, prospective open label interventional proof-of-concept trial in 15 patients with active BU. Visual function was evaluated by both qualitative and quantitative outcome measurements. As a secondary objective, we evaluated the utility of new outcome measures in detecting disease activity.

METHODS AND MATERIALS

Trial design and oversight

We report the 1-year results of the HLA-A29 trial. We included BU patients to be treated for a maximum of 3 years with subcutaneous injections of abatacept (Orencia, prefilled syringe 125 mg/mL) in a prospective open label interventional proof-of-concept study in two Belgian hospitals (University Hospitals Leuven (sponsor) and ZNA Middelheim, Antwerp (participating site)).

Trial participants

Patients who were 18 years of age or older and had a diagnosis of active BU and carried the HLA-A29 allele were eligible to participate in the trial. The key inclusion criteria were active disease characterised by at least one active inflammatory choroidal or retinal vascular lesion, or vitreous haze (VH) grade of 1+ or higher (according to National Eye Institute (NEI) criteria adapted by the Standardization of Uveitis Nomenclature Working Group; scores range from 0 to 4+, with higher scores indicating greater severity of uveitis).^{34,35} The full inclusion and exclusion criteria are provided in online supplemental file 1.

Treatment

At least 1 week before the baseline visit, all patients had to stop all concomitant immunosuppressive drugs, for example, corticosteroids, methotrexate, mycophenolate mofetil, azathioprine, tacrolimus, sirolimus or cyclosporine A.

The investigational medical product abatacept was shipped by Bristol Myers Squibb to the pharmacy of University Hospitals of Leuven and ZNA Middelheim Antwerp. Abatacept was supplied in prefilled syringes and was administered subcutaneously. Abatacept injections for subcutaneous administration, 125 mg/mL, are ready-to-use solutions provided in prefilled siliconised syringes. No additional drug preparation is required prior to administering to patients. A sufficient amount of abatacept is incorporated into each syringe so that each syringe can deliver the labelled amount of 1 mL on administration.

At the baseline visit, patients were instructed to inject the drug subcutaneously by the study nurse. The first injection was done at the baseline visit under supervision of the study nurse. Afterwards, patients injected themselves at home.

Patients received the syringes on the visit dates, supplying them for the period until the next visit. Patients collected the empty syringes in a dedicated needle container and returned the syringes at the visit dates, where the syringes were counted.

Study visits and end points

During the first year of the trial, clinic visits were scheduled to occur at screening; at baseline; at weeks 6, at weeks 12, at months 6, 9 and 12 (online supplemental file 2). Patients' conditions were evaluated until the determination of treatment failure. The maximum duration of treatment is 156 weeks.

The primary efficacy end point was the time-to-treatment failure at or after week 6. Patients were considered to have treatment failure if they met any one of the following criteria in at least one eye: worsening of best corrected visual acuity (BCVA) by 15 or more letters on the Early Treatment Diabetic Retinopathy

Table 1 Clinical characteristics of patients in the population

Patients, n	15
Demographics	
Age (years)	
Mean±SD (N)	54.65±8.87 (15)
Median, range (min, max)	58.70, (37.00, 65.00)
(95% CI)	(49.74 to 59.56)
Gender	
Male	40.00% (6/15)
Female	60.00% (9/15)
BCVA ETDRS letters at baseline	
Mean±SD (N)	82.47±8.05 (30)
Median, range (min, max)	84.00, (51.00, 93.00)
(95% CI)	(79.46 to 85.47)
Duration of diagnosis before the trial (months)	
Mean±SD (N)	25.60±34.73 (15)
Median, range (min, max)	12.00, (2.00, 120.00)
(95% CI)	(6.37 to 44.83)
Treated with corticosteroids before the trial	80.00% (12/15)
How long were corticosteroids stopped before the trial? (months)	
Mean±SD (N)	18.17±35.48 (12)
Median, range (min, max)	1.00, (0.00, 116.00)
High-dose corticosteroids within 6 months before enrolment*	26.67% (4/15)
Corticosteroids-sparing drugs before the trial	
Any corticosteroid-sparing treatment	73.33% (11/15)
Duration of corticosteroid-sparing treatment (months)	
Mean±SD (N)	25.73±34.31 (11)
Median, range (min, max)	13.00, (1.00, 120.00)
Cyclosporine A	63.64% (7/11)
Mycophenolate mofetil	27.27% (3/11)
Sirolimus	9.09% (1/11)
Methotrexate	27.27% (3/11)
*Equivalent of prednisolone 1 mg/kg and/or periocular or intravitreal corticosteroid injection.	
BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.	

Study (ETDRS) chart, 30% increase of central retinal thickness (CRT) on optical coherence tomography (OCT) relative to baseline, 2-step increase in VH grade relative to baseline, new active inflammatory choroidal (detected on Indocyanine Green Angiography (ICGA)) and/or inflammatory retinal vascular lesions relative to baseline (detected on Fluorescein Angiography (FA)).

Eight ranked secondary end points, related to disease state, were tested: change in VH grade in each eye, change in BCVA (logarithm of the minimum angle of resolution) in each eye, time to OCT evidence of macular oedema in at least one eye, change in CRT in each eye, change in central choroidal thickness (CCT) in each eye, change in NEI Visual Function Questionnaire—25 (VFQ-25) composite score and sub scores, change in Dual FA-ICGA Score, as defined by the Angiography Scoring for Uveitis Working Group³⁶ and changes in full-field electroretinography (ERG).

All ranked secondary end points were analysed by a comparison of the value at baseline with the value at the final study visit in the first year of the trial.

All patients who received at least one dose of abatacept were included in the safety analysis. Adverse events were monitored and reported from the time the first dose of abatacept was administered. Data on serious adverse events were collected

starting from the time of informed consent. At every study visit, adverse events were determined by blood analysis (testing renal and liver function and full blood count) (online supplemental file 3) and by adverse event reporting.

Procedures

The schedule of trial procedures is available in online supplemental file 2. The presence or absence of inflammatory choroidal or retinal vascular lesions was determined by dilated indirect ophthalmoscopy and by FA and ICGA, using the Heidelberg Scanning LASER fluorescein and ICG angiography (Heidelberg Engineering). VH was assessed by means of dilated indirect ophthalmoscopy and was graded with the use of Standardization of Uveitis Nomenclature Working Group—adapted NEI criteria.^{34 35} OCT was performed with the Zeiss Cirrus 5000 (Carl Zeiss Meditec) OCT. For each eye, a macular cube slab 512×128 and 2 HD 5 lines raster (1 on 180° and 1 on 90°) with enhanced depth imaging (EDI) were taken, centred on the fovea. CRT was measured on the macular cube slab central on the fovea. CCT was measured using the EDI mode of the Zeiss Cirrus 5000 OCT (HD 5 lines raster). Scoring of dual FA and ICGA was based on images captured with the Heidelberg Scanning LASER FA and ICGA (Heidelberg Engineering). Full-field ERG was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) protocols.³⁷ Quantitative values, such as 30 Hz implicit time and amplitude, as well as amplitude and latency of a and b waves were analysed.

Statistical analysis

Efficacy end points were analysed in the intention-to-treat data set. For all patients, the time-to-treatment failure (the primary end point) and the time to OCT evidence of macular oedema (a secondary end point) were based on the first eye to meet the criteria. All end points were analysed in each eye, except for the VFQ—25, which was analysed on a patient basis.

For the eye-level parameters, in order to accommodate for the covariance structure of the paired design (two eyes per patient), a mixed model for repeated measures was performed, with the mean-standardised baseline value of the parameter as covariate, and the change from baseline at 12 months as the dependent variable, with the subject identity added as subject level effect and a compound symmetry covariance structure.

A proportional hazards model was fitted to estimate the HR with its 95% CI. The time-to-treatment failure due to each component of the primary end point and the time to macular oedema were analysed in the same way. Other ranked secondary end points were evaluated by the paired Student’s t-test to test changes from baseline.

Enrolled patients had active disease. Therefore, qualitative and quantitative outcome measurements were expected to worsen if patients were left untreated. Our a priori definition of drug effectiveness was a stabilisation or improvement in at least 50% of patients after 1 year.

Patient information was summarised descriptively, continuous variables were compared by paired student’s t-test. Adverse events that occurred during treatment were summarised descriptively. All statistical tests were two-sided, and P values of less than 0.05 were considered to indicate statistical significance. Analyses were performed by the investigators with SAS software, V.9.4. The data reported here reflect the 1-year trial data.

RESULTS

Patients

Fifteen BU patients with active disease were included in the trial. The enrolment of patients started on 24 June 2019 and was completed on 11 December 2020. The mean duration of diagnosis before enrolment in the trial was 25.6 months. The mean age was 54.7 years. All patients were Caucasians (100%) with a female preponderance (60%). Mean BCVA at baseline was 82.47 ETDRS letters. (table 1)

Before enrolment, 12 patients were treated with high-dose corticosteroids (equivalent of prednisolone 1mg/kg and/or periocular or intravitreal corticosteroid injections) that were tapered and stopped completely before the baseline visit. Four patients had a recent diagnosis and were treated with high doses of corticosteroids within 6 months before enrolment: three of these patients were started on high doses of oral corticosteroids within 6 months before enrolment that were tapered and stopped before enrolment in the trial; the other patient was treated with an intravitreal injection with triamcinolone in the left eye and a subconjunctival injection with betamethasone in the right eye 2 months before enrolment, because of macular oedema. Three patients did never receive corticosteroid treatment: in one patient, corticosteroids were not administered because of diabetes mellitus, this patient was treated directly with methotrexate. Two patients with a recent diagnosis did not receive any immunosuppressive treatment before enrolment. Eleven patients were treated with at least one type of chronic classic immunomodulatory treatment: details are reported in table 1.

Efficacy

Four patients did not complete the study until year 1. Of these four patients, two patients had treatment failure with new active retinal vascular lesions at the 3-month visit in one patient and a recurrence of macular oedema with more than 30% increase in retinal thickness in the left eye at the 9-month visit in another patient. One patient withdrew consent at the 6-month endpoint. The fourth patient had a branch retinal vein occlusion in the left eye at the year one endpoint, which was reported as an adverse event. Three out of four patients (75%) who left the trial within the first year were treated with high doses of corticosteroids within 6 months before enrolment in the trial.

Several ranked secondary end points related to disease state were evaluated.

Table 2 distinguishes outcome measures with and without statistically significant improvement at the year 1 endpoint.

Figure 2 shows the evolution of different outcome measures (CCT, FA Score, ICGA Score and dual FA-ICGA) during the first year of the trial and the correlation between CCT and dual FA-ICGA Score after 6 months and after 1 year.

Figure 3 illustrates changes in dual FA-ICGA scores after 1 year of treatment with abatacept.

Safety

Adverse events were reported in 12 out of 15 patients. Among the adverse events reported, 13 events were labelled by investigators as ‘possibly related’ to the trial intervention. There were no serious adverse events reported in this trial. The most frequently reported adverse events were fatigue and headache. No cancers were reported in the study group. One patient had COVID-19 during the first year of the trial. This patient interrupted the drug until full recovery. All patients received COVID-19 vaccinations without interference with the study drug (online supplemental file 4).

Only one adverse event: a branch retinal vein occlusion in one eye led to discontinuation of participation in the trial. In this patient, the causal relationship was judged as unlikely because uncontrolled arterial hypertension probably was a major risk factor.

Patients had serial lab analyses at the study visits. There were no clinically significant problems detected and reported.

DISCUSSION

In this proof-of-concept trial, treatment with subcutaneous injections of abatacept was proven to be effective and showed significant improvement of numerous objective and subjective measurement outcomes of visual function, compared with the baseline visit. All patients had active disease at baseline. In 11 patients the disease was still active despite chronic classic immunomodulatory therapy (IMT). The fact that we observed significant improvement after suspension of classic IMT in favour of abatacept seems to indicate that the latter drug is more effective than classic IMT (figure 3.1, 3.2, 3.4 and 3.5).

In the first year of the trial, only two patients had treatment failure. These patients both had a recent diagnosis and were treated with high doses of corticosteroids within 6 months before enrolment. It has been described that BU patients who received

Table 2 Distinguishes outcome measures with and without statistically significant improvement at the year 1 endpoint.

Statistically significant (95% CI)	Not statistically significant (95% CI)
Vitreous haze grading (p=0.0014) (-1.45 to -0.47)	Best corrected visual acuity (p=0.8354) (-1.58 to 1.92)
Central choroidal thickness (p=0.0011) (-83.16 to -27.61)	Central retinal thickness (p=0.3549) (-35.40 to 13.81)
Fluorescein Angiography (FA) Score (p=0.0014) (-5.00 to -1.58)	Electroretinography flicker implicit time (p=0.3852) (-2.60 to 1.08)
Indocyanine Green Angiography (ICGA) Score (p<0.001) (-17.60 to -12.38)	
Dual FA-ICGA Score (p<0.001) (-22.73 to -14.68)	
Visual Function Questionnaire—25 overall composite Score (p=0.0032) (3.43 to 13.16)	
General vision subscale (p=0.0055) (5.42 to 24.58)	General health subscale (p=0.1039) (-2.01 to 18.68)
Specific mental health subscale (p=0.0089) (3.03 to 16.77)	Ocular pain subscale (p=0.2360) (-4.72 to 17.22)
Specific role difficulties subscale (p=0.0045) (5.97 to 25.28)	Near activities subscale (p=0.2227) (-3.42 to 13.15)
Colour vision subscale (p=0.0271) (1.99 to 27.18)	Distance activities subscale (p=0.1022) (-1.9 to 17.07)
	Driving subscale (p=0.1527) (-4.48 to 24.48)
	Specific dependency subscale (p=0.4292) (-3.50 to 7.67)
	Peripheral vision subscale (p=0.3889) (-9.08 to 21.58)
	Specific social functioning subscale (p=0.0527) (-0.09 to 12.59)

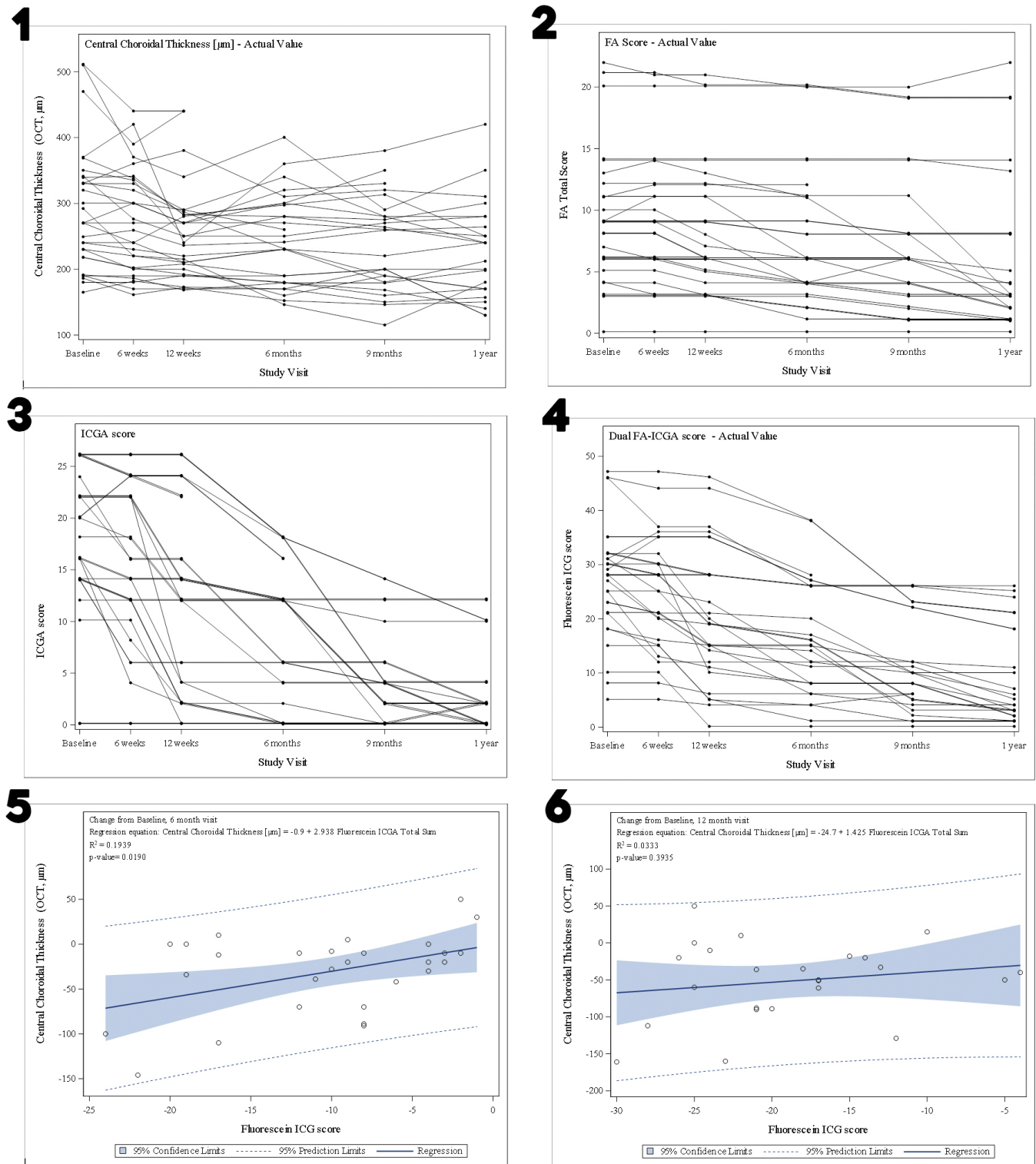


Figure 2 (A) Evolution of CCT in time (per eye). (B) Evolution of FA Score in time (per eye). (C) Evolution of ICGA Score in time (per eye). (D) Evolution of Dual FA-ICGA Score in time (per eye). (E) Correlation between CCT and Dual FA-ICGA Score at 6 months. (F) Correlation between CCT and Dual FA-ICGA Score at 12 months.

longer duration of IMT prior to remission had less chance of relapse than those with shorter duration of IMT. Further, those patients who received oral or periocular corticosteroids were significantly associated with risk of relapse.³⁸ Probably, treatment failure in these patients can be explained by a rebound phenomenon after tapering and stopping corticosteroids before

enrolment, that was not sufficiently compensated by abatacept. To evaluate the pure effect of abatacept, we decided to treat only with abatacept and not to overlap with a burst of corticosteroids with mandatory tapering. However, as with all immunomodulatory and biological drugs, it takes some time for subcutaneous abatacept to reach its maximal effect.³⁹

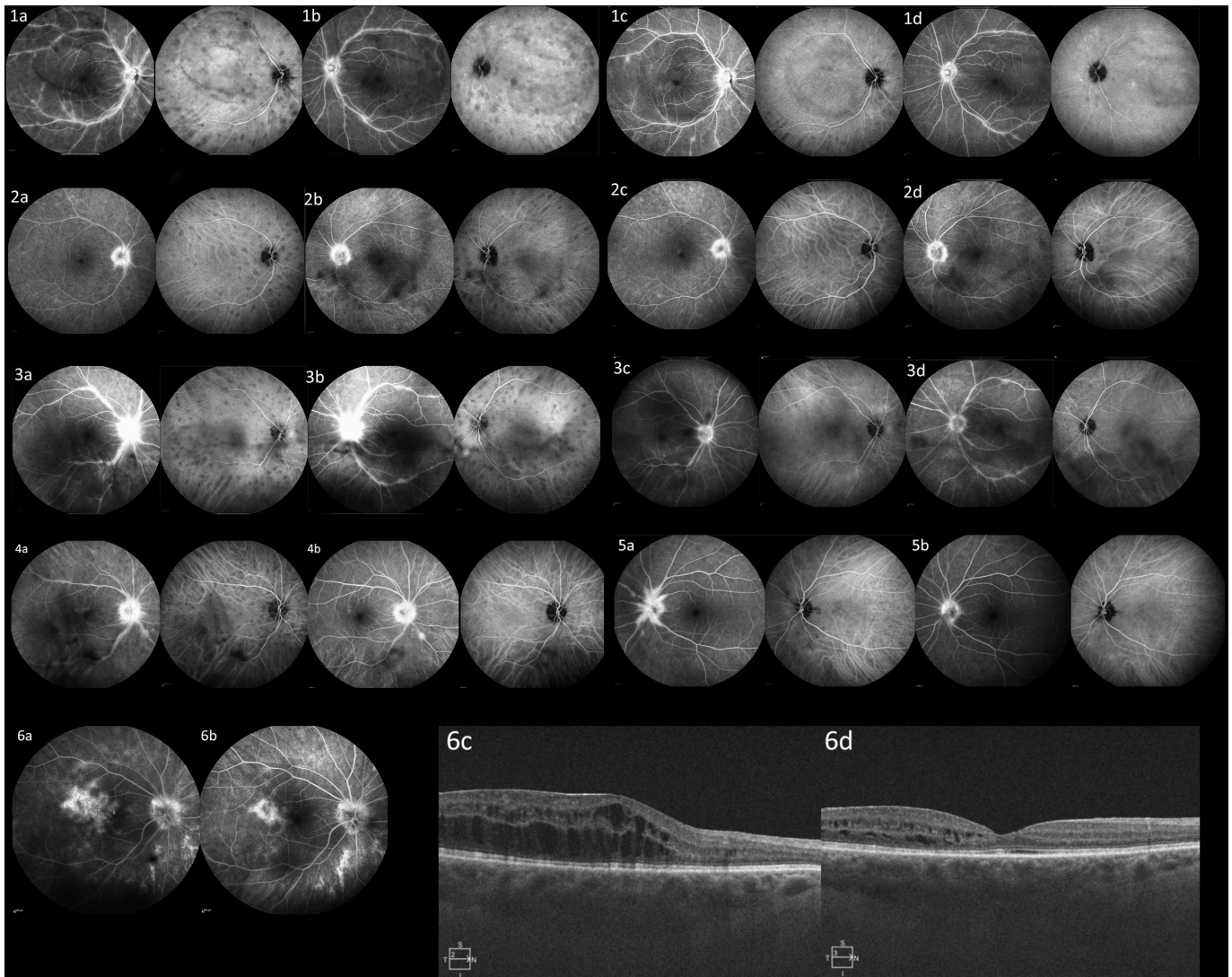


Figure 3 Fluorescein Angiography (FA) and Indocyanine Green Angiography (ICGA) images are shown at baseline and after 1 year for six different patients. (1a) At baseline right eye (RE) dual FA-ICGA Score 35. (1b) At baseline left eye (LE) dual FA-ICGA Score 35. (1c) After 1-year RE dual FA-ICGA Score 18. (1d) After 1-year LE dual FA-ICGA Score 18. (2a) At baseline RE: dual FA-ICGA Score 23. (2b) At baseline LE: dual FA-ICGA Score 21. (2c) After 1-year RE: dual FA-ICGA Score 11. (2d) After 1-year LE: dual FA-ICGA Score 1. (3a) At baseline RE: dual FA-ICGA Score 28. (3b) At baseline LE: dual FA-ICGA Score 28. (3c) After 1-year RE: dual FA-ICGA Score 8. (3d) After 1-year LE: dual FA-ICGA Score 9. (4a) At baseline RE: dual FA-ICGA Score 25. (4b) After 1-year RE: dual FA-ICGA Score 4. (5a) At baseline LE: dual FA-ICGA Score 15. (5b) After 1-year LE: dual FA-ICGA Score 1. (6a) At baseline: FA shows macular oedema. (6b) After 1 year: FA shows less extensive macular oedema. (6c) At baseline: extensive macular oedema on OCT. (6d) After 1 year: regression of macular oedema on OCT.

Three patients did not receive any corticosteroids before enrolment in the trial. They all responded to abatacept, with gradual improvement of both retinal vasculitis and choroiditis, with diminishing hypofluorescent dark dots (HDD) (figure 3.3 and 3.6). Although the trial sample is too small to draw conclusions in this regard, further research to evaluate the exact role for corticosteroids in BU is warranted.

As in most uveitis trials, patients were considered to have treatment failure if they met any one of the criteria as mentioned in the methods and materials section. In BU, visual acuity is often preserved,⁴⁰ macular oedema often does not involve the centre of the macula and VH is not pronounced. Therefore, these criteria are not very reliable to determine treatment failure or to monitor disease. The fourth criterion of new vascular lesions is more adequate but is a qualitative assessment. Therefore, there is a clear unmet need for quantitative appraisal.⁴¹

In this trial, the secondary objective was to evaluate different outcome measurements of visual function to monitor the disease. Our results confirm that BCVA is not a good parameter to determine activity. Most patients had preserved visual acuity and there were no statistic changes on treatment with abatacept, despite improvement of numerous other parameters. Similarly, most of the patients did not have macular oedema affecting the fovea. Although there was some improvement in selected cases (figure 3.6), overall, there was no significant difference in CRT at the 1-year visit, compared with the baseline visit. There was a significant improvement in VH, but all patients had a low grade of VH at enrolment (≤ 2), with limited impact on visual acuity. In BU, retinal vasculitis predominantly affects the large retinal vessels along the arcades. Therefore, evaluating large-vessel perivascular thickness on OCT scans might be a better method for non-invasively monitoring posterior pole large-vessel retinal

vasculitis,^{42–44} but extensive small vessel leakage can occur and will only be detected by FA.

On the contrary, CCT was significantly reduced after 1 year of treatment. This is in line with previous studies that showed that choroidal thickness is increased in early active disease and can decrease with effective treatment.^{45–49} In this trial, there was a clinically significant correlation between the change in CCT and change in total dual FA-ICGA Score after 6 months of treatment, but not at the 12-month timepoint (figure 2). This might reflect that CCT is an adequate non-invasive measurement to determine treatment response in early, active disease. However, with abatacept the choroid seems to thin during the first 6 months of treatment, but then reaches a plateau, whereas the ICGA Score and consequently the dual FA-ICGA Score continue to improve. This might implicate that CCT is less reliable to monitor chronic disease.

Several authors have stressed the importance of ICGA to evaluate choroiditis in BU.^{50–55} To quantify both retinal and choroidal inflammation for uveitis, the dual FA-ICGA Score was defined and evaluated by the Angiography Scoring for Uveitis Working Group.^{36 41 56} The downside of dual FA-ICGA scoring is that it is invasive with intravenous administration of dyes. In this trial, dual FA-ICGA Score was measured at all visits, showing significant improvement after 1 year of treatment with abatacept. As illustrated in figure 2, there was a rapid improvement of choroiditis with less HDD, reflected by the ICGA Score and a slightly slower and less extensive improvement of retinal vasculitis, reflected by FA Score. Interestingly, choroiditis achieved complete remission in most patients, treated with abatacept. This finding suggests that abatacept might be very promising to treat diseases with stromal choroiditis.

ERG is another examination that can be used to evaluate retinal function and to monitor BU. More specifically, an increased 30Hz implicit time seems to correlate with retinal vasculitis and to reflect ongoing disease activity.^{57–66} We could not confirm this finding, as the 30Hz implicit time did not reach significance after 1 year of treatment, neither did any other ERG parameter. Furthermore, ERG is technically demanding and very uncomfortable to the patient.

Subjectively, the VFQ-25, noticed a significant improvement in general vision and some subscales, but not for the near and distance activities subscale. This is in line with the well-preserved visual acuity until late in the disease process.

The subcutaneous injections with abatacept were well tolerated by all study subjects. There were no adverse events, related to the injection, reported. There were no serious adverse events reported, but one patient developed a branch retinal vein occlusion in one eye, which led to discontinuation of the trial for this subject. The causal relation with abatacept was estimated as unlikely because of the presence of a major risk factor of uncontrolled arterial hypertension. The reported adverse events were in line with those in the literature, with headache and fatigue as the most frequently described adverse events. There were no cancers reported during the trial.

As discussed by Kuiper *et al*, probably all patients with BU carry the HLA-A29 allele. However, the presence of HLAA29 itself is not enough to develop the disease. HLA-A29 confers a major risk factor, but probably there is another trigger that activates CD8+ T cells.⁸ The trigger is not known, but infectious agents or an oncogenic trigger have been proposed.⁹

Recently, a case of birdshot-like uveitis was described in an HLA-A29 negative patient treated with immune checkpoint inhibitors for melanoma.⁶⁷ This article raised the question whether BU is the result of an autoimmune reaction triggered by

neoplastic (skin) changes.^{68 69} According to this theory, a processed neoplastic antigen is presented by the antigen presenting cell on the surface of the HLA A29 molecule, resulting in activation of T cells. This cellular immune response is targeted to the inciting tumour cells, but might cross-react with ocular structures, such as choroidal melanocytes. This theory has been suggested before by Hassman *et al*, who demonstrated the presence of antimelanoma antibodies in the serum of BU patients.⁷⁰

If this theory holds true, the inciting immune response for BU is a protective immune response to fight cancer and melanoma in particular. Treatment with IMT is beneficial to treat uveitis but might increase the risk to develop (skin) cancer. This is a very important consideration, when abatacept is used. Abatacept blocks stimulation of both CD4+ and CD8+ T cells. CD8+ T cells are important in tumour immune surveillance. Blocking these cells might increase the chance to develop cancer and especially melanoma. In RA treated with abatacept, recent analyses for specific cancer sites showed a significantly increased relative OR for melanoma (1.58 (95% CI 1.17 to 2.08)), but not for other specific cancer sites.⁷¹ In BU, the risk might even be higher, considering a possible pathophysiologic role for melanoma cells in this disease. Therefore, protective measures to avoid exposure to the sun and vigilance seem warranted.

Limitations

This trial has the advantage to study only one disease, in contrast to most uveitis trials where different diseases causing uveitis are lumped together. However, due to the limited sample size, it is difficult to extrapolate our findings to all patients with BU. The small sample size also hampers robust conclusions on safety and the short duration of 1 year follow-up makes it impossible to evaluate long-term effects.

Not all outcome measures that were described in the literature were evaluated. To limit the burden to the patient, we did not test the visual field, nor contrast sensitivity. Therefore, we cannot correlate our findings with these functional tests.

CONCLUSION

Abatacept is a highly effective drug to treat BU. Both choroiditis and retinal vasculitis improved significantly with treatment.

Classic outcome measures in uveitis trials, such as BCVA and CRT, are inadequate to monitor disease activity, in contrast to CCT to evaluate choroiditis in early active disease and the dual FA-ICGA Score to determine retinal vasculitis and choroiditis in a quantitative and reproducible way.

Abatacept was well tolerated and there were no safety issues during the trial, but vigilant follow-up to detect cancer and more specifically melanoma is important.

Acknowledgements We would like to thank graphic illustrator Ivo De Wispelaere for creating figure 1 and for editing figures 2 and 3. We also want to thank study nurses Lies Prové and Sarah Neale for their support.

Contributors The trial was designed by PPS, CPH, PAK and KdV. The investigators PPS and JVC collected the data and PPS conducted the data analyses. All the authors had full access to the data. All the authors reviewed and provided feedback on all manuscript drafts and made the decision to submit the manuscript for publication. PPS is guarantor.

Funding The trial was sponsored by the University Hospitals of Leuven. The pharmaceutical company Bristol Myers Squibb supplied a grant to the sponsor (IM101-794) and supplied the medication to the sponsor and the participating sites.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved by Ethics Committee University Hospitals Leuven: approval OG032, Ethics Committee

ZNA Middelheim: approval 5190, and the trial was performed in compliance with the provisions of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines and applicable local regulations. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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Supplementary files

Supplementary file 1: INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

1. Subject is at least 18 years of age.
2. Subject is diagnosed with BU, HLA A 29+
3. Subject must have active disease at the Baseline visit as defined by the presence of at least 1 of the following parameters in at least one eye :
 - Active, inflammatory, chorioretinal and/or inflammatory retinal vascular lesions
 - $\geq 1+$ vitreous haze (National Eye Institute [NEI]/SUN criteria)
4. Subjects who do not have previous, active or latent tuberculosis (TB). Subjects with negative QuantiFERON®-TB Gold test (or interferon-gamma release assay (IGRA) equivalent) are eligible. Subjects with a repeat indeterminate QuantiFERON®-TB Gold test (or IGRA equivalent) result are not eligible. The TB screening tests are diagnostic tests. In the event of a negative TB screening test, the results are to be interpreted in the context of the patient's epidemiology, history, exam findings, etc. and it is the responsibility of the investigator to determine if a patient has previous, active or latent tuberculosis or not. Under no circumstances can a patient with a positive QuantiFERON®-TB Gold test (or IGRA equivalent) enter the study.

Exclusion criteria

1. Subject with prior inadequate response to high-dose oral corticosteroids (>30 mg of prednisolone or equivalent)
2. Subject with confirmed or suspected infectious uveitis, including but not limited to infectious uveitis due to TB, cytomegalovirus (CMV), Human T-Lymphotropic Virus Type 1 (HTLV-1), Whipple's disease, Herpes Zoster virus (HZV), Lyme disease, toxoplasmosis and herpes simplex virus (HSV).
3. Subject with corneal or lens opacity that precludes visualization of the fundus or that likely requires cataract surgery during the duration of the trial.
4. Subject with intraocular pressure of ≥ 25 mmHg and on ≥ 2 glaucoma medications or evidence of glaucomatous optic nerve injury.
5. Subject with Best Corrected Visual Acuity (BCVA) less than 20 letters (Early Treatment Diabetic Retinopathy Study) in at least one eye at the Baseline Visit.
6. Subject with intermediate uveitis or panuveitis that has signs of intermediate uveitis (e.g. presence or history of snowbanking or snowballs) and symptoms and/or magnetic resonance imaging (MRI) findings suggestive of a demyelinating disease such as multiple sclerosis. All subjects with intermediate uveitis or panuveitis that have signs of intermediate uveitis (e.g., presence or history of snowbanking or snowballs) must have had a brain MRI within 90 days prior to the Baseline Visit.
7. Subject has had previous exposure to anti-tumor necrosis factor (TNF) therapy or any biologic therapy (except intravitreal anti-vascular endothelial growth factor [VEGF] therapy) with a potential therapeutic impact on non-infectious uveitis

8. Subject with exposure to classic immunosuppressive therapy, in which the dose has been increased within the last 28 days prior to Baseline visit or is within the following doses at the screening visit: Methotrexate (MTX) >25 mg per week Cyclosporine > 4 mg/kg per day Mycophenolate mofetil >2 grams per day or an equivalent drug to mycophenolate mofetil (e.g. mycophenolic acid) at an equivalent dose approved by the Medical Monitor. Azathioprine > 175 mg per day Tacrolimus (oral formulation) >8 mg per day.
9. Subject is still on immunosuppressive therapy (Corticosteroids, Methotrexate, Cyclosporine, Mycophenolate Mofetil, Azathioprine, Tacrolimus, Sirolimus) at the baseline visit.
10. Subject has received Iluvien® (glucocorticosteroids implant) within 3 years prior to the Baseline visit or that has had complications related to the device. Subject has had Iluvien® (glucocorticosteroids implant) removed within 90 days prior to the Baseline visit or has had complications related to the removal of the device.
11. Subject has received intraocular or periocular corticosteroids within 30 days prior to Baseline visit.
12. Subject with proliferative or severe non-proliferative diabetic retinopathy or clinically significant macular edema due to diabetic retinopathy. Subject with neovascular/wet age-related macular degeneration Subject with abnormality of vitreo-retinal interface (i.e., vitreomacular traction, epiretinal membranes, etc.) with the potential for macular structural damage independent of the inflammatory process. Subject with severe vitreous haze that precludes visualization of the fundus at the Baseline visit.
13. Subject has received Ozurdex® (dexamethasone implant) within 6 months prior to the Baseline visit. Subject has received intravitreal anti-VEGF therapy within 45 days of the Baseline visit for Lucentis® (ranibizumab) or Avastin® (bevacizumab) or within 60 days of the Baseline visit for anti-VEGF Trap (aflibercept).
14. Subject has received intravitreal methotrexate within 90 days prior to the Baseline visit
15. Subject on systemic carbonic anhydrase inhibitor within 1 week prior to Screening visit.
16. Subject with macular edema as the only sign of uveitis.
17. Subject with a history of scleritis.
18. Subject on cyclophosphamide within 30 days prior to the Baseline visit.
19. Subjects with a known HIV, HepB/C infection.
20. Subjects with an active or recent acute infection.
21. Subjects with a history of chronic or recurrent bacterial, viral or systemic fungal infections.
22. Subjects with malignancies.
23. Subjects who have received any live vaccines within 3 months of the start of the study drug.

Supplementary file 2: STUDY VISITS

1. Screening visit:

Informed consent

Inclusion/Exclusion

Tuberculosis screening using QuantiFERON®-TB Gold test (or interferon-gamma release assay (IGRA) equivalent)

Pregnancy test in women of Childbearing age

2. Visit week 0:

Adverse event reporting

Concomitant Medication

BCVA: Best corrected Visual Acuity

VH grading: Vitreous Haze Grading

OCT: Optical Coherence Tomography

FA-ICGA: Fluorescein Angiography-Indocyanine Green Angiography

ERG: Electroretinography

Visual Q: Visual Questionnaire

LAB test: hematology-kidney-liver function

Injection Training will be given

Medication will be given for treatment at home

3. Visit week 6:

Adverse event reporting

Concomitant medication

BCVA: Best corrected Visual Acuity

VH grading: Vitreous Haze Grading

OCT: Optical Coherence Tomography

FA-ICGA: Fluorescein Angiography-Indocyanine Green Angiography

LAB test: hematology-kidney-liver function

Medication will be given for treatment at home

4. Visit week 12:

Adverse event reporting

Concomitant medication

BCVA: Best corrected Visual Acuity

VH grading: Vitreous Haze Grading

OCT: Optical Coherence Tomography

FA-ICGA: Fluorescein Angiography-Indocyanine Green Angiography

LAB test: hematology-kidney-liver function

Medication will be given for treatment at home

5. Visit month 6

Adverse event reporting

Concomitant medication

BCVA: Best corrected Visual Acuity

VH grading: Vitreous Haze Grading

OCT: Optical Coherence Tomography

FA-ICGA: Fluorescein Angiography-Indocyanine Green Angiography

ERG: Electroretinography

Visual Q: Visual Questionnaire

LAB test: hematology-kidney-liver function

Medication will be given for treatment at home

6. Visit month 9

Adverse event reporting

Concomitant medication

BCVA: Best corrected Visual Acuity

VH grading: Vitreous Haze Grading

OCT: Optical Coherence Tomography

FA-ICGA: Fluorescein Angiography-Indocyanine Green Angiography

LAB test: hematology-kidney-liver function

Medication will be given for treatment at home

7. Visit month 12

Adverse event reporting

Concomitant medication

BCVA: Best corrected Visual Acuity

VH grading: Vitreous Haze Grading

OCT: Optical Coherence Tomography

FA-ICGA: Fluorescein Angiography-Indocyanine Green Angiography

ERG: Electroretinography

Visual Q: Visual Questionnaire

LAB test: hematology-kidney-liver function

Pregnancy test in women of Childbearing age

Medication will be given for treatment at home

Supplementary file 3: LABORATORY TESTS

Laboratory measurements: full blood counts, liver and kidney function will be performed at each visit in the hospital labs of the study centers.

The following lab tests will be performed:

Hemoglobin
Erythrocytes/Htc
Thrombocytes
Leucocytes
White Blood Cell Differentiation
Urea
Creatinin
Sodium
Potassium
AST
ALT
Alk. Phosphatase
Gamma GT

Before the study, at the screening visit, a pregnancy test will be done in female patients of childbearing age (blood test) and an IGRA test (T-spot or Quantiferon blood test) and HIV/Hepatitis B (HBsAg/anti-HBc/anti-HBs)/Hepatitis C serology will be performed in all patients.

Supplementary file 4. ADVERSE EVENTS

Adverse Event	Population
Total N	N=15
Incidence of Any Adverse Event	
Total Incidence	12

Incidence of Any Adverse Event by Grouped Symptom / Described Symptom	
Other Symptoms Category	10
fatigue	4
COVID-19	1
dizziness	1
impetigo	1
nausea	1
pathological fracture metatarsal bone right foot	1
tooth Problem	1
diarrhea	1
branch retinal vein occlusion with secondary macular edema left eye	1
subacromial bursitis left shoulder	1
secondary cataract left eye	1
urinary tract infection	1
blepharitis	1
vertigo and tendency to faint	1
arterial hypertension	1
Pain Symptoms	6
headache	3
back pain	1
neck pain	1
pain right foot	1
pain right hip	1
painful joints	1
Respiratory Symptoms	2
cough	1
upper respiratory tract inflammation	1