



**HAL**  
open science

# Anti-TNF $\alpha$ dans les uvéites chroniques non infectieuses : une étude observationnelle rétrospective à propos de 151 patients

Pierre-Antoine Quintart

## ► To cite this version:

Pierre-Antoine Quintart. Anti-TNF $\alpha$  dans les uvéites chroniques non infectieuses : une étude observationnelle rétrospective à propos de 151 patients. Human health and pathology. 2023. dumas-04279460

**HAL Id: dumas-04279460**

**<https://dumas.ccsd.cnrs.fr/dumas-04279460>**

Submitted on 23 Feb 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

#### IMPORTANT : OBLIGATIONS DE LA PERSONNE CONSULTANT CE DOCUMENT

Conformément au *Code de la propriété intellectuelle*, nous rappelons que le document est destiné à un **usage strictement personnel**. Les "analyses et les courtes citations justifiées par le caractère critique, polémique, pédagogique, scientifique ou d'information" sont autorisées sous réserve de mentionner les noms de l'auteur et de la source (article L. 122-4 du *Code de la propriété intellectuelle*). Toute autre représentation ou reproduction intégrale ou partielle, faite sans le consentement de l'auteur ou de ses ayants droit, est illicite.

---

De ce fait, nous vous rappelons notamment que, **sauf accord explicite** de l'auteur de la thèse ou du mémoire, **vous n'êtes pas autorisé** à rediffuser ce document sous quelque forme que ce soit (impression papier, transfert par voie électronique, ou autre). Tout contrevenant s'expose aux peines prévues par la loi.

**NANTES UNIVERSITÉ**

---

**FACULTÉ DE MÉDECINE**

---

Année : 2023

N°

**THÈSE**

pour le

**DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE**

OPHTALMOLOGIE

par

***Pierre-Antoine QUINTART***

---

Présentée et soutenue publiquement le 29 septembre 2023

---

**Anti-TNF $\alpha$  dans les uvéites chroniques non infectieuses : une étude  
observationnelle rétrospective à propos de 151 patients**

---

Président : Monsieur le Professeur Michel WEBER

Directeur de thèse : Docteur Hélène MASSE

Membres du Jury :

- Docteur Chloé COURET
- Docteur Julie GRAVELEAU

## REMERCIEMENTS

*À mon Jury*, je dédie une profonde reconnaissance.

À Monsieur le Professeur Michel Weber : merci de m'avoir fait l'honneur de présider ce Jury. Je rêve de parvenir à accumuler toutes les connaissances qui sont vôtres, si cela se peut.

À ma directrice de thèse, Madame la Docteur Hélène Massé : merci pour ta rigueur sans failles qui a constitué un cadre bienveillant idéal pour m'épanouir dans ce travail. Merci pour tes enseignements qui en trois mois de consultations m'ont tant apporté sur la prise en charge non seulement des uvéites, mais surtout des patients eux-mêmes.

À Madame la Docteur Julie Graveleau : merci pour votre accompagnement (et l'immense coup de pouce initial) et votre rigueur également. Je souhaite un jour être le sujet d'autant d'éloges de la part des patients que vous aujourd'hui !

À Madame la Docteur Chloé Couret : bien que l'internat soit finalement trop court pour m'avoir offert l'opportunité de passer un semestre avec toi, je garderai des souvenirs mémorables des temps universitaires partagés autour de TRIOZ (quelle épopée !), de la bartonnellose... merci pour ta gentillesse permanente, preuve – si elle était nécessaire – que discuter de quinoa ou de vacances ou que d'aller boire une bière, ne sont pas des obstacles à l'expression d'un profond respect mutuel.

Merci bien sûr au Docteur Matthieu Wargny et à la Clinique des données du CHU de Nantes pour l'exploitation de l'entrepôt de données eHOP.

*Une pensée à tous les internes, médecins, aides-soignants, infirmiers, orthoptistes, secrétaires, étudiants, et j'en passe...* Que ce soit à Poitiers, à Nantes, au Mans, à Saint-Nazaire : une liste exhaustive ne serait qu'un mirage, mais merci pour tous ces fous rires et cette entraide collective indispensables en ces temps de crise pour l'hôpital public !

Je pense bien sûr en particulier à tous mes co-internes avec qui nous avons vécu des aventures hilarantes (« Fac de Naaaantes ! »), à mes partenaires de promo, aux rétiniologues en herbe pour nos discussions enflammées sur le futur de la rétine (discussions certes favorisées par quelques coupes de champagne), aux médecins avec qui j'ai été en stage.

*À Yann et Brivael* : sans appel merci à mes mentors qui m'ont fait grandir chirurgicalement, merci pour votre pédagogie et votre bonne humeur permanente. Quoi qu'il arrive, je sais que nos chemins se croiseront régulièrement. Yann, j'espère un jour peeler des membranes avec la rapidité et la sérénité qui sont tiennes...

*À tous mes chers amis d'enfance*, qui même si nous ne nous voyons pas autant que je le souhaiterais, restent présents après tant d'années comme si le temps s'était figé : Simon, JB, Grégoire, Sébastien... à toutes nos aventures passées, et à celles à venir ! Merci pour votre patience au cours de ces années ô combien chronophages. En particulier pensée à mon meilleur pote, Florian le Jojo national : merci pour tout bro' !

*À mes amis de Fac*, merci pour tous ces moments à vos côtés. Roxane et toutes tes crèmes (une vraie dermato !), Anouk et ton soutien en toutes circonstances (même quand on ne t'annonce plus que 300 mètres à parcourir...), Willi et ta philosophie de vie (Jul RPZ), Romain et ta résilience permanente, Dodo *aka* la reine des potins... Je vous aime, vivement nos nouvelles péripéties !

*À mes amis d'internat* bien sûr.

Camille : merci pour ces deux belles années remplies de souvenirs impérissables. Même si nos chemins ont divergé je ne désespère pas de refaire un tour de vélo comme si rien n'était arrivé !

Cécilia, Louis : merci pour vos conseils avisés sur les mousquetons en titane et les poussettes. Merci à César d'éclairer votre quotidien (et finalement un peu le nôtre), j'espère qu'il fera au moins l'effort de lire cette thèse à l'âge de raison.

Elo, Phiphi : merci pour votre présence, vos discordes sources de fous rires (tiens, tiens, le Vercors...). Bon, on est en 2023 maintenant, c'est pour quand le mariage ?

Julie : merci ma chère Julie pour ton écoute attentive de tous mes doutes – cela valait bien quelques tomes de One Piece entachés de bière, sans doute. Continue à nous divertir le plus longtemps possible avec tes histoires du camp d'été... et passe le bonjour à ta maman !

Loïc : merci d'être la personne lumineuse que tu incarnes chaque jour. Entre tes t-shirts si particuliers, ton amour des tchoutch, quelques souvenirs (si tu les as conservés) du Marlowe, on obtient une personnalité éclectique mais si rayonnante !

Momo, l'asticot, la Momotrice : merci de sans cesse dynamiser notre groupe par ton enthousiasme et ta créativité sans failles... toujours dispo pour retourner voir des lucioles avec toi.

Romain : merci au pro des lasagnes de nous avoir tant sustentés, de nous avoir tant fait rire de par tes mauvais mensonges au loup-garou, ou frissonner d'admiration par le remplissage de tes manches de t-shirt par des bras si musclés !

Et merci à tous les autres bien sûr : Béatrice ; Arnaud, Basile et Sarah pour ces centaines de kilomètres à fouler le sentier côtier ou le bord de l'Erdre (je serais déçu de ne jamais partager un marathon tous les trois !)..

### *À ma famille.*

Mes aïeux, que vous vieilliez sur moi depuis là-haut ou depuis votre téléphone ou votre tablette : j'espère parvenir à vous rendre fiers. Même si la distance et la folle course du temps nous séparent, je pense fort à vous !

Comment ne pas finir une telle litanie de remerciements par les plus évidents : Maman, Papa, Paul, je vous dois tellement que des pages entières ne suffiraient pas à vous exprimer ma gratitude. Puissé-je un jour vous rendre ne serait-ce qu'au centième tout ce que vous m'avez apporté. Alors tout simplement, et sincèrement, merci. Merci pour votre soutien indéfectible au cours des années quels que soient mes choix ; pour tous vos sacrifices ; pour vos conseils avisés (même si j'ai parfois eu du mal à l'avouer !) ; pour les valeurs que vous m'avez inculquées ; pour la curiosité et la passion du monde et des êtres humains que vous avez fait germer par toutes nos pérégrinations ; merci pour tous ces petits plats préparés, pour votre réconfort dans les moments de stress ou de moral au plus bas. Vous avez été, êtes et serez toujours mon point d'ancrage, un phare dans l'obscurité profonde des années de médecine et dans la vie ; et finalement, le garde-fou pour ne pas sombrer dans tous les travers et péchés qui peuvent en découler. J'espère que vous serez fiers de ce qu'est devenu le monstre qui se roulait par terre au restaurant ou urinait sur des vitrines. Paul – petit frère (plus si petit hélas !), courage pour ces derniers mois d'externat. Que les années à venir t'offrent tout l'épanouissement que tu mérites.

*Enfin, merci à vous, lecteurs,* pour votre motivation à venir à bout de ces remerciements interminables. Puisse la suite être à la hauteur de votre patience !

Pierre-Antoine

(PAQ pour les intimes)

((2PAQ [2Pac] pour les plus drôles))

(((PA, tout simplement)))

## SUMMARY

<b>INTRODUCTION</b> .....	<b>1</b>
<b>METHODS</b> .....	<b>4</b>
Study design and population.....	4
Study endpoints.....	4
Anti-TNF administration and follow-up.....	5
Statistical analysis .....	5
<b>RESULTS</b> .....	<b>7</b>
Baseline characteristics .....	7
Anti-TNF therapies characteristics .....	8
Adjuvant therapies and corticosteroid sparing.....	9
Efficacy.....	10
Visual acuity .....	10
Central macular thickness .....	12
Laser Flare Meter.....	14
Vasculitis.....	15
Visual field.....	17
Recurrences.....	17
Treatment duration.....	18
Safety .....	20
<b>DISCUSSION</b> .....	<b>21</b>
<b>BIBLIOGRAPHY</b> .....	<b>25</b>
<b>SUPPLEMENTARY MATERIALS</b> .....	<b>33</b>
Supplementary material S1.....	33
Supplementary material S2.....	34
Supplementary material S3.....	38
Supplementary material S4.....	39
Supplementary material S5.....	40
Supplementary material S6.....	41
Supplementary material S7.....	42
Supplementary material S8.....	43
Supplementary material S9.....	45
<b>INDEX</b> .....	<b>46</b>
Tables index.....	46
Figures index .....	46

## ACRONYMS AND ABBREVIATIONS

AAA: antibodies against adalimumab

AE(s): adverse event(s)

CMT: central macular thickness

GNEDS: groupe nantais d'éthique dans le domaine de la santé

IL-1/-17: interleukin 1/17

IPMN: intraductal papillary mucinous neoplasm

JIA: juvenile idiopathic arthritis

LFM: laser flare meter

LogMAR: logarithmic minimum angle of resolution

M1/M3/M6/M12/M24: month 1/3/6/12/24

MD: mean deviation

ME: macular edema

MMF: mycophenolate mofetil

MRI: magnetic resonance imaging

NF- $\kappa$ B: nuclear factor-kappa B

NIU: non-infectious uveitis

NSAID: non-steroidal anti-inflammatory drug

OCT: optical coherence tomography

SD: standard deviation

TACE: TNF- $\alpha$  converting enzyme

TGF- $\beta$ : transforming growth factor  $\beta$

TNF: tumor necrosis factor

- TNFRI/II: TNF receptors type I/II
- sTNF: soluble TNF
- tmTNF: transmembrane TNF

VA: visual acuity

VEGF: vascular endothelial growth factor



## ABSTRACT

### **Anti-TNF therapies in non-infectious uveitis: an observational retrospective study about 151 patients**

**Objective:** the aim of this study was to assess real-world efficacy and safety of anti-TNF therapies in patients with chronic or recurrent non-infectious uveitis.

**Methods:** patients were retrospectively included in this monocentric study in the University Hospital of Nantes. Data were collected when available before initiation of the treatment, one month after (M1), at M3, M6, M12, and M24. We collected demographic information (gender, age), data about the treatment (type, indication), its efficacy (distance visual acuity (VA), laser flare meter (LFM), central macular thickness (CMT), presence of retinal vasculitis, visual field in case of Birdshot chorioretinopathy), and its safety.

**Results:** 151 patients were included in the study (160 treatments). Most participants were women (60%) with a mean age of  $46 \pm 17$  years. Usually, used anti-TNF therapy was adalimumab (90%) for inflammation (56%), as a second-line of corticosteroid-sparing therapy (54%). This resulted in significant corticosteroid tapering, with a median dose dropping from 10 mg at baseline to 5 mg at the last known visit, allowing tapering below 7 mg a day in 80% of the patients. Less than a third of the patients had idiopathic uveitis, and the main part of the diagnosis were sarcoidosis, Birdshot chorioretinopathy, Behçet's disease, or rheumatologic diseases. CMT and LFM decrease were statistically significant at each appointment. VA significantly improved from M6 onward. We also observed an improvement of the vasculitis rate, and of the Mean Defect on the visual field in case of Birdshot chorioretinopathy. We found no significant new safety concerns, the main adverse events reported being pain or cutaneous effects, with few serious infections. Prudence is still needed anyway about tuberculosis reactivation or demyelination. 70% of the patients who stopped the treatment for remission did not relapse.

**Conclusion:** this study highlights real-life efficacy and safety of anti-TNF therapies.

**KEYWORDS:** anti-TNF, chronic non-infectious uveitis, real-world.

## INTRODUCTION

Uveitis is the inflammation of the uvea. The SUN workshop (1) (supplementary material S1), defined its type depending on the anatomical involvement (anterior, intermediate, posterior, or panuveitis), the onset (sudden or insidious), the duration (limited, or persistent over 3 months), the course (acute, recurrent in case of episodes separated by inactivity periods without any treatment of more than 3 months, and chronic in case of relapse before 3 months after discontinuing the treatment).

This study concerns recurrent and chronic non-infectious uveitis (NIU). That involves ruling out differential diagnosis, especially infectious uveitis, or masquerade syndromes (2). According to the etiology (3), patients can either have only ophthalmologic signs (Birdshot chorioretinopathy, multifocal choroiditis...) or may also have systemic signs (sarcoidosis for example).

Any ocular inflammation may be complicated by inflammatory macular edema (ME), which can lead to acute vision loss and even legal blindness. Few studies (4) describe the worldwide epidemiology of uveitis, one of the latest and biggest being Thorne's (5) in the United States: based on 4 million patients of medico-administrative databases, there were 133 uveitis for 100,000 adults, mainly non-infectious (91%) and anterior (81% of NIU). In the literature, the prevalence varies from 38 to 284 for 100,000 inhabitants, and the incidence from 17 to 52 per 100,000 person-years (6,7). ME is frequent, in one third of cases (8), even more in chronic uveitis (9); and serious, leading up to 42% of acute vision loss (10). It is the fifth leading cause of blindness in young patients aged 20 to 65 years (11), with important quality of life and medico-economic consequences (12,13).

Uveitic ME is a multifactorial process (supplementary material S2) resulting mostly from the activation of nuclear factor-kappa B (NF- $\kappa$ B) (14) in the innate immunity pathway, which induces cytotoxic and vasogenic components. The cytotoxic part is due to alterations of microglia, and macroglia as well with Müller cells' dysfunction. The vasogenic part is due to the blood-retinal barrier breakdown (15), involving many pro-inflammatory cytokines (16) such as vascular endothelial growth factor (VEGF), TNF- $\alpha$ , IL-1, TGF- $\beta$ ; or angiotensin II, adenosine, histamine, glucose... Several cofactors can also interact with these: vitreomacular traction, macular ischemia, chronic ME sequelae with Müller cells' apoptosis, inflammatory choroidal neovascularization, contiguity with papillary swelling...

At the moment, many treatments can be used in recurrent and chronic NIU according to the presence of ME, the diagnosis, unilaterality of the disease, previous local or systemic treatments, patient's medical history, patient choice... Some algorithms have thus been

proposed (16,17) (supplementary material S3), beginning to determine the place of anti-TNF therapies: immediately in case of short-time vision-threatening conditions (severe retinal vasculitis, severe Behçet's disease), as a 2<sup>nd</sup>-line therapy in case of corticoreistant uveitis, or as a 3<sup>rd</sup>-line therapy in case of high-level corticodependent uveitis (after immunosuppressants or immunomodulators: methotrexate, cyclosporine, azathioprine, mycophenolate mofetil...).

Used now for some years in rheumatoid arthritis (first approval of Humira® in the United States in 2002 (18)) or inflammatory bowel diseases, these biotherapies have been gradually adopted for treating chronic NIU, especially in France since adalimumab's approval in 2017 (19). Tumor Necrosis Factor (TNF) is a pleiotropic inflammatory cytokine produced by macrophages and lymphocytes, and in the eye by microglia, Müller cells, and retinal pigment epithelium. Synthesized TNF is expressed as a transmembrane protein (tmTNF) which is split by TNF- $\alpha$  Converting Enzyme (TACE) (20), a matrix metalloproteinase called ADAM17, to release soluble TNF (sTNF). Then both tmTNF and sTNF bind to type I (TNFRI also called p55/CD120a) and type II receptors (TNFRII also called p75) (21) expressed by iris, ciliary body, and retina cells. It induces several signaling pathways: transcription factor activation (nuclear factor- $\kappa$ B), proteases (caspases), protein kinases (MAP kinases)... which activate inflammatory and immune cells, thus leading to apoptotic pathways and cytokines releasing. Monoclonal anti-TNF antibodies inhibit the binding of TNF to TNFRI and II with high affinity, so the cytokine production, and lead to apoptosis of TNF-expressing cells (except for certolizumab) (supplementary material S4) (22–24).

Adalimumab is a fully human recombinant immunoglobulin G1 anti-TNF monoclonal antibody (25), the only one authorized and the most used in France (17). Its efficacy has been proven in many studies, such as VISUAL I (active uveitis) (26), II (inactive uveitis) (27), and III (long-term efficacy and safety) (28). It was also shown in Juvenile Idiopathic Arthritis (JIA) in addition to methotrexate, in ADJUVITE (29) and SYCAMORE (30) trials. An 80 mg subcutaneous injection can be administered the first week, then since the 2<sup>nd</sup> week a 40 mg injection every 2 weeks (31), except in case of weight under 30 kg (half doses). Its use is allowed for treating non-infectious intermediate, posterior uveitis or panuveitis, in adults with insufficient response to corticosteroids, requiring corticosteroids sparing, or for whom corticosteroids are inappropriate. Its use is also allowed for treating chronic non-infectious anterior uveitis in children aged 2 and over, with methotrexate, in case of insufficient response or intolerance to conventional treatment or for whom conventional treatment is inappropriate.

Etanercept, a fully human soluble TNF receptor fusion protein, is not used anymore because of a lack of intraocular penetration with poor efficacy compared to other molecules

and even a risk of uveitis under treatment (32,33). This could be linked to the bound of soluble TNF receptors type II to transmembrane TNF- $\alpha$  which could prolong the half-life of TNF (34).

Some other anti-TNF therapies are also sometimes prescribed in uveitis, such as infliximab, certolizumab or golimumab, but their use is off label with fewer studies supporting them. However, according to experts' opinion, infliximab could be used in case of failure of adalimumab, which is supported by several studies with efficacy of both treatments (17,35,36), even if adalimumab may have better outcomes in some subgroups such as Behçet's disease (37). Finally, biosimilars are also more and more prescribed (38), significantly reducing costs.

Despite all data that we have nowadays, some questions are still relevant: what is their real-life efficacy in reducing central macular thickness, flare, or vasculitis? Should we favour an anti-TNF therapy over another one? Even if the discontinuation of the treatment could be considered after 1 to 2 years (17), which duration is to prefer and are there relapses afterward? To bring some answers, we decided to perform a retrospective monocentric study in the University Hospital of Nantes.

## METHODS

### **Study design and population**

This monocentric descriptive retrospective study focused on patients aged 17 or over, with a medical follow-up in the University Hospital of Nantes, treated by anti-TNF therapy for recurrent or chronic NIU.

Patients were recruited either by our team (consecutive patients in the ophthalmology or internal medicine departments), or thanks to the Clinic Data Center by using the University Hospital of Nantes local data warehouse eHOP, with six arbitrary keywords (TNF, adalimumab, Humira, Amgevita, Hulio, Remicade), from 01/01/2011 to 16/04/2023.

Patients were not included in case of lack of data from the initiation of the treatment to 24 months after, especially if the number of appointments was 2 or less. The use of etanercept was also a non-inclusion criterion given that it can induce uveitis.

The GNEDS (Groupe Nantais d'Ethique dans le Domaine de la Santé), an ethics committee, gave a favorable ethical opinion.

### **Study endpoints**

Data were collected about:

- The population: demographic information (gender, age).
- The treatment and its indication: type of uveitis, etiology, line of therapy, associated treatments including local adjuvant corticotherapy, treatment frequency and duration, discontinuation and why.
- The efficacy of the treatment, for the eyes with uveitis only: visual acuity (VA) (distance decimal VA with Monoyer scale), laser flare meter (LFM), central macular thickness (CMT) (thickness of the central 1000  $\mu\text{m}$ ) in optical coherence tomography (OCT) (on Heidelberg Spectralis® tomograph), presence of retinal vasculitis (clinically obvious or angiographic vasculitis [staining and/or pooling and/or occlusion] of large vessels on Heidelberg Spectralis® tomograph), mean deviation (MD) on the visual field (Octopus 900®) in case of Birdshot chorioretinopathy, number of recurrences in case of HLA-B27 associated uveitis... VA over 10/10 was assigned by default to the values 10/10 to avoid fluctuations (sometimes VA over 10/10 being not assessed). Hyalitis was not a criterion because of the imprecision of data (vitreous cells or haze not specified) and inter-observer variability.
- The safety of the treatment: occurrence of any adverse event (AE), with a particular interest in serious infections (needing intravenous antibiotics and/or surgical treatment or any hospitalization), in malignancy, and in cutaneous effects.

Efficacy and safety data were collected if available (to the nearest month) before initiation of the treatment, one month after (M1), and at M3, M6, M12, M24.

Data were retrospectively extracted from medical records of patients in ophthalmology (software Softalmo® by Corilus) and in other medical specialties, especially internal medicine or rheumatology (software Millennium/Power Chart® by Cerner corporation). Optical coherence tomography and angiography data (CMT, presence of vasculitis) were checked on the Heidelberg Eye Explorer® software (SPECTRALIS Software V7.0.01).

### **Anti-TNF administration and follow-up**

A pre-therapeutic evaluation was almost systematically performed with physical examination, control of the vaccinations, and laboratory tests (such as QuantiFERON® to exclude any risk of tuberculosis reactivation (39)).

Given the risk of Central Nervous System demyelination with these therapies (40–42), a magnetic resonance imaging (MRI) was done for non-anterior uveitis, especially in case of chronic intermediate uveitis of which multiple sclerosis is a major etiology.

Usually, patients were followed up in multidisciplinary consultations, with particular attention paid in internal medicine to their information and therapeutic education (risk of infection, sun protection...). The follow-up was standardized and reproducible between different practitioners.

### **Statistical analysis**

Statistical analyses were performed using the EXCEL® Software.

Qualitative data are presented as counts and percentages. Quantitative variables are presented as mean ± standard deviation (SD) for normally distributed data, or as median and range (minimum-maximum values) for others.

Survival curves were made according to Kaplan-Meier method for the probability of discontinuation of the treatment over time, based on R software with Biostatgv website (43).

Unfortunately, VA was recorded as decimal data. To analyze it, even if it is not as accurate, we had no choice but to transform it into logarithmic minimum angle of resolution (LogMAR) by using reference charts (44) and the next formula (45):

$$\text{LogMAR} = -\text{Log}(\text{decimal visual acuity}).$$

Main continuous variables (distance VA, CMT, LFM) were analyzed with paired samples Student's t-tests based on R software, also thanks to Biostatgv website (43), making sure of effectives greater than 30.

P-values are 2-sided, and the threshold for statistical significance was set to  $p < 0.05$ .

Data are rounded to the nearest unit (percentages, CMT), tenth (mean daily corticotherapy dose, treatment time and time to relapse, risk of recurrence), hundredth (VA, LFM, MD) or thousandth (p-values).

We did subgroup analyses for the 5 main etiologies.

## RESULTS

### Baseline characteristics

Baseline data are summarized in Table 1. A total of 151 patients were included in the study (flow chart in supplementary material S5) with a total use of 160 anti-TNF therapies (9 patients have had 2 different anti-TNF therapies).

Most participants were women (60%) with a mean age of  $46 \pm 17$  years.

There were only 26 unilateral uveitis (17%), with half of them of rheumatologic etiologies (JIA or HLA-B27). Panuveitis and posterior uveitis were prevailing anatomical types (respectively 40% and 36%).

Less than a third of the patients had idiopathic uveitis. Sarcoidosis and sarcoidosis-like disease, Birdshot chorioretinopathy, Behçet and Behçet-like disease represented the main part of the diagnosis (almost 40% for all), and so were rheumatologic diseases (almost 20%) with JIA and HLA-B27 associated uveitis.

Ten patients were lost to follow-up, among which 5 before any discontinuation of the treatment.

**Table 1.** Baseline demographics and clinical characteristics of the patients.

	<b>Patients treated by anti-TNF (n = 151)</b>
<b>Age in years, mean <math>\pm</math> SD</b>	46 $\pm$ 17
<b>Women, n (%)</b>	90 (60)
<b>Bilateral uveitis<sup>1</sup>, n (%)</b>	125 (83)
<b>Type of uveitis, n (%)</b>	
Panuveitis	61 (40)
Posterior uveitis	54 (36)
Intermediate uveitis	5 (3)
Intermediate / posterior uveitis	4 (3)
Anterior uveitis	27 (18)
<b>Diagnosis, n (%)</b>	
Idiopathic/unknown	45 (30)
Sarcoidosis or sarcoidosis-like disease	25 (17)
Birdshot chorioretinopathy	23 (15)
JIA	19 (13)
. For ophthalmologic reasons	15 (10)
. For ophthalmologic and rheumatologic reasons	4 (3)
HLA-B27 associated uveitis	11 (7)
Behçet or Behçet-like disease	11 (7)
Idiopathic multifocal choroiditis	4 (3)
Others <sup>2</sup>	13 (9)

<sup>1</sup>: one unilateral uveitis was a one-eyed patient.

<sup>2</sup>: others include serpiginous choroiditis (n = 3), multiple sclerosis (n = 3), Vogt-Koyanagi-Harada disease (n = 2), sympathetic ophthalmia (n = 2), lymphoma (n = 1), occlusive vasculitis (Takayasu's arteritis, n = 1), rheumatoid arthritis (n = 1).



## Anti-TNF therapies characteristics

The main anti-TNF therapy used was adalimumab (Table 2), in particular Humira®, with injections every 2 weeks but up to 8 weeks (supplementary material S6). The main indication of anti-TNF therapy was inflammation for half of the patients, and a combined indication of inflammation and ME for almost a third of them. Only 3 anti-TNF were begun for a systemic reason. It was the same excluding anterior uveitis (52% of inflammation, 33% of inflammation associated with ME, 9% of ME).

Anti-TNF were often used as a second-line therapy, for half of them after methotrexate.

**Table 2.** Characteristics of used anti-TNF therapies.

	<b>Anti-TNF used (n = 160)</b>
<b>Anti-TNF therapy used, n (%)</b>	
<b>Adalimumab</b>	<b>144 (90)</b>
. Humira®	112 (70)
. Hulio®	16 (10)
. Amgevita®	13 (8)
. Imraldi®	3 (2)
<b>Infliximab</b>	<b>7 (4)</b>
. Remicade®	5 (3)
. Remsima®	1 (1)
. Inflectra®	1 (1)
<b>Certolizumab – Cimzia®</b>	<b>4 (3)</b>
<b>Golimumab – Simponi®</b>	<b>5 (3)</b>
<b>Indication of anti-TNF therapy, n (%)</b>	
Inflammation	90 (56)
ME	12 (8)
Inflammation associated with ME	46 (29)
Intolerance to another medicine	3 (2)
Others <sup>1</sup>	9 (6)
<b>Line of corticosteroid-sparing therapy, n (%)</b>	
First-line <sup>2</sup>	41 (26)
Second-line	87 (54)
Third-line	18 (11)
Fourth-line	9 (6)
Fifth-line	5 (3)
<b>In case of 2<sup>nd</sup>-line therapy, type of 1<sup>st</sup>-line, n (% of 2<sup>nd</sup>-line)</b>	
Methotrexate	40 (46)
Azathioprine	23 (26)
Mycophenolate mofetil (MMF)	18 (21)
Colchicine	3 (3)
Others <sup>3</sup>	3 (3)

<sup>1</sup>: others include systemic indication, non-compliance to another treatment, association of intolerance with inflammation or ME or both.

<sup>2</sup>: one of them did not even have any corticosteroid before initiation of the anti-TNF therapy.

<sup>3</sup>: others include interferon alfa-2a (n = 1), tocilizumab (n = 1), Humira® (n = 1).

## Adjuvant therapies and corticosteroid sparing

Anti-TNF therapies allowed an important corticosteroid sparing: in patients still treated by systemic corticotherapy (Table 3), median daily dose decreased from 10 mg at initiation to 5 mg at the last known visit. Anti-TNF enabled a corticosteroid tapering below 7 mg a day in 80% of the patients. Local adjuvant corticotherapy was used in 28% of the patients.

About half of the patients had concomitant systemic treatment, mainly methotrexate (28%). This rate remained stable until the last known visit.

**Table 3.** Characteristics of used adjuvant therapies.

	Patients treated by anti-TNF (n = 151)
<b>Adjuvant local corticotherapy during evolution, n (%)</b>	42 (28)
Subconjunctival triamcinolone injection(s) only	11 (7)
Intravitreal dexamethasone injection(s)	31 (21)
. Only	18 (12)
. Associated with intravitreal fluocinolone acetonide	3 (2)
. Associated with subconjunctival triamcinolone	9 (6)
. Associated with both	1 (1)
<b>Daily corticotherapy dose (mg) at anti-TNF initiation, median [min – max]</b>	10 [0 – 120]
<b>Adjuvant systemic corticotherapy at the last visit<sup>1</sup>, n (%)</b>	71 (47)
In patients with corticotherapy:	
Sparing < 7 mg a day, n (% of these patients)	57 (80)
Sparing < 5 mg a day, n (% of these patients)	48 (68)
Daily dose (mg), median [min – max]	5 [1 – 60]
<b>Systemic treatments during evolution, n (%)</b>	74 (49)
Azathioprine	12 (8)
Colchicine	2 (1)
Interferon alfa-2a – Pegasys®, Roferon-A®	1 (1)
Methotrexate	43 (28)
MMF	11 (7)
MMF then colchicine	1 (1)
MMF associated with interferon alfa-2a	1 (1)
Colchicine associated with another treatment <sup>2</sup>	3 (2)
<b>Systemic treatments associated at the last visit<sup>1</sup>, n (%)</b>	70 (46)
Azathioprine	5 (3)
Colchicine	3 (2)
Interferon alfa-2a – Pegasys®, Roferon-A®	5 (3)
Methotrexate	27 (18)
MMF	8 (5)
Sarilumab	2 (1)
Tocilizumab	7 (5)
Tocilizumab associated with methotrexate	4 (3)
Others <sup>3</sup>	9 (6)

<sup>1</sup>: the last visit is the last known appointment, whether or not anti-TNF are still being used.

<sup>2</sup>: including 2 patients with azathioprine, 1 with methotrexate then MMF.

<sup>3</sup>: including patients treated by MMF associated to colchicine or interferon or tocilizumab, chemotherapy (with rituximab), methotrexate associated to sarilumab, ocrelizumab, rituximab, tecfidera, ustekinumab.

## Efficacy

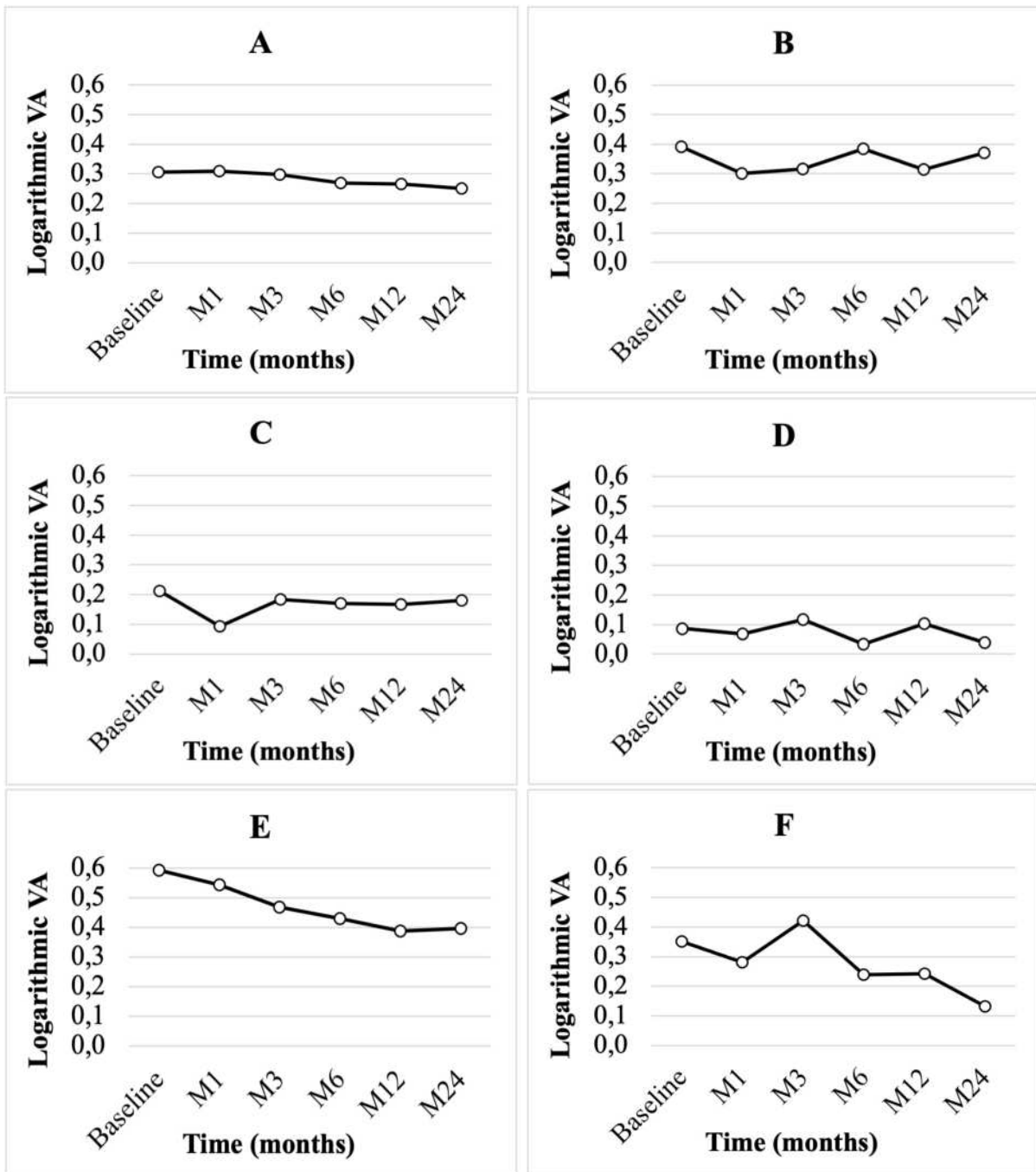
### *Visual acuity*

VA improved from baseline to M24 (Table 4, Figure 1A), with significant differences from M6 onward ( $p = 0.007$ ). This was more important in Behçet/Behçet-like disease subgroup (Figure 1E) and JIA subgroup (Figure 1F).

**Table 4.** Changes in logarithmic VA (LogMAR) from baseline to M24.

VA	Logarithmic VA, mean $\pm$ SD	Available paired data, n (%)	Logarithmic VA differences versus baseline, mean [95% CI]	p-value
Baseline	0.31 $\pm$ 0.49	/	/	/
M1	0.31 $\pm$ 0.51	143 (49)	0.04 [-0.01; 0.09]	0.148
M3	0.30 $\pm$ 0.52	216 (74)	0.03 [-0.01; 0.07]	0.164
M6	0.27 $\pm$ 0.52	210 (72)	0.07 [0.02; 0.12]	<b>0.007</b>
M12	0.27 $\pm$ 0.54	237 (81)	0.06 [0.01; 0.12]	<b>0.025</b>
M24	0.25 $\pm$ 0.53	204 (70)	0.07 [0.02; 0.12]	<b>0.012</b>

*All 292 eyes were included when data were available, and all available paired data were analyzed for calculating the differences compared to baseline.*



**Figure 1.** Changes in mean logarithmic VA from baseline to M24.

- A. Overall changes
- B. Changes in idiopathic uveitis subgroup
- C. Changes in sarcoidosis/sarcoidosis-like disease subgroup
- D. Changes in Birdshot chorioretinopathy subgroup
- E. Changes in Behçet/Behçet-like disease subgroup
- F. Changes in JIA subgroup

### **Central macular thickness**

Central macular thickness significantly improved as soon as the first month ( $p = 0.006$ ) and increasingly so over time (Table 5, Figure 2A). Mean CMT thus decreased from 339  $\mu\text{m}$  at baseline to 297  $\mu\text{m}$  at M24 (mean decrease of 13%).

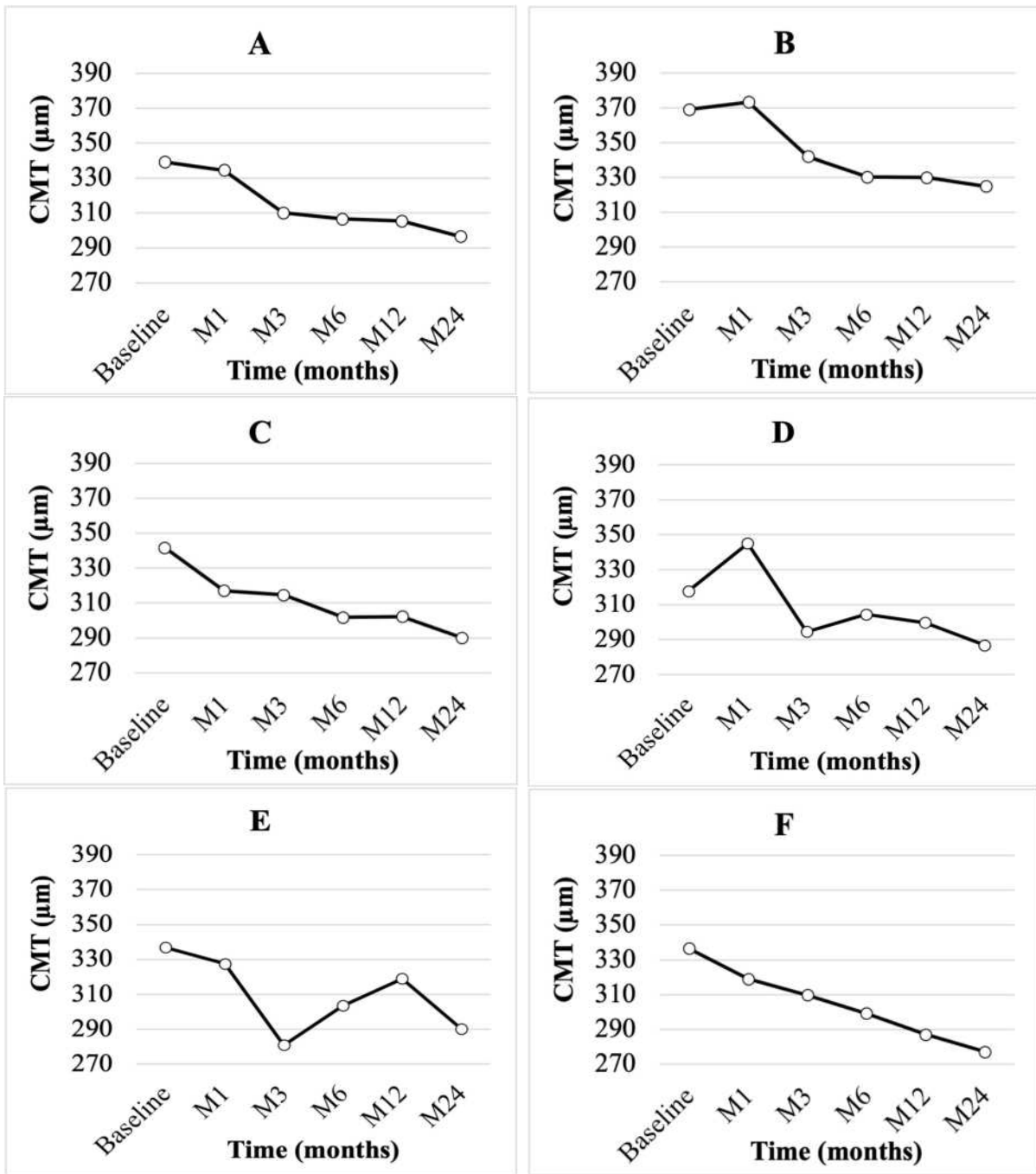
17% of the eyes decreased more than 20% of their CMT under treatment, and 22% reached a CMT below 260  $\mu\text{m}$ .

There was not much difference in the relative CMT reduction between subgroups (Figures 2B to 2F). Supplementary materials S7A and S7B show the changes in CMT in patients treated initially for ME.

**Table 5.** Changes in CMT from baseline to M24.

<b>CMT</b>	<b>CMT, mean <math>\pm</math> SD (<math>\mu\text{m}</math>)</b>	<b>Mean decrease versus baseline, %</b>	<b>Rate of CMT <math>\leq 260</math> <math>\mu\text{m}</math>, %</b>	<b>Rate of CMT <math>\leq 300</math> <math>\mu\text{m}</math>, %</b>	<b>Available paired data, n (%)</b>	<b>CMT differences versus baseline, mean [95% CI]</b>	<b>p-value</b>
Baseline	339 $\pm$ 103	/	16	42	/	/	/
M1	334 $\pm$ 109	1	13	47	132 (45)	18 [5; 31]	<b>0.006</b>
M3	310 $\pm$ 78	9	17	55	214 (73)	29 [18; 39]	<b>&lt; 0.001</b>
M6	307 $\pm$ 67	10	15	53	201 (69)	40 [28; 51]	<b>&lt; 0.001</b>
M12	305 $\pm$ 76	10	17	58	233 (80)	37 [26; 48]	<b>&lt; 0.001</b>
M24	297 $\pm$ 64	13	22	62	196 (67)	45 [30; 59]	<b>&lt; 0.001</b>

*All 292 eyes were included when data were available, and all available paired data were analyzed for calculating the differences compared to baseline.*



**Figure 2.** Changes in mean CMT from baseline to M24.

- A. Overall changes
- B. Changes in idiopathic uveitis subgroup
- C. Changes in sarcoidosis/sarcoidosis-like disease subgroup
- D. Changes in Birdshot chorioretinopathy subgroup
- E. Changes in Behçet/Behçet-like disease subgroup
- F. Changes in JIA subgroup

### ***Laser Flare Meter***

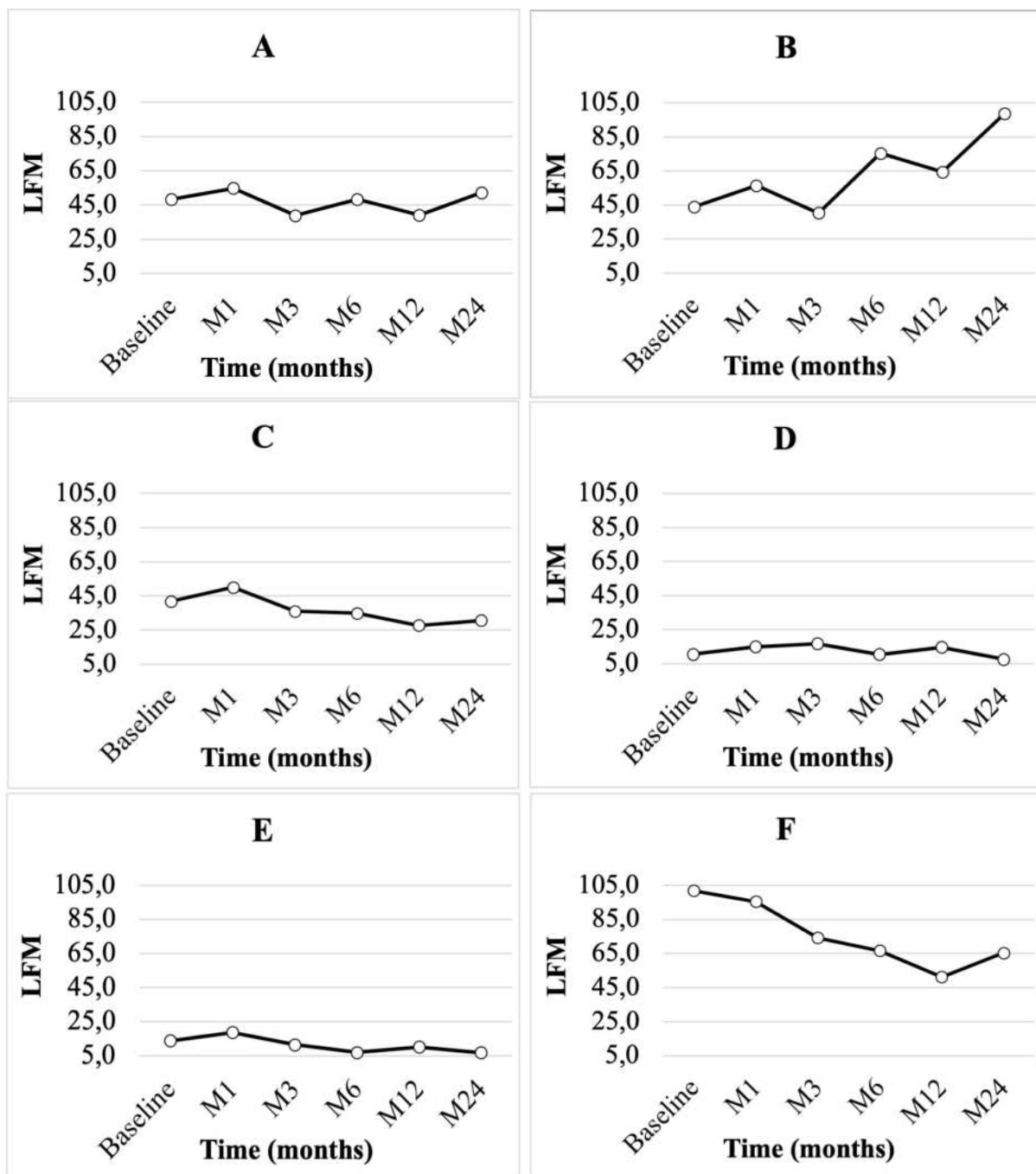
Laser Flare Meter also significantly improved from M1 onward ( $p = 0.040$ ), and increasingly so over time (Table 6, Figure 3).

However, this depended a lot of the subgroup: we observed a normal LFM throughout the evolution for Birdshot chorioretinopathy or Behçet/Behçet-like disease (Figures 3D and 3E), a clear improvement in patients with JIA despite the baseline higher level (Figure 3F), and at the other end a degradation of LFM in idiopathic uveitis subgroup (Figure 3B).

**Table 6.** Changes in LFM from baseline to M24.

<b>LFM</b>	<b>LFM, <i>mean ± SD</i></b>	<b>Available paired data, <i>n (%)</i></b>	<b>LFM differences <i>versus</i> baseline, <i>mean [95% CI]</i></b>	<b>p-value</b>
Baseline	48.34 ± 70.97	/	/	/
M1	45.75 ± 94.71	66 (23)	12.80 [0.63; 24.97]	<b>0.040</b>
M3	38.81 ± 73.03	110 (38)	10.14 [1.71; 18.57]	<b>0.019</b>
M6	48.40 ± 83.19	89 (30)	15.67 [5.39; 25.95]	<b>0.003</b>
M12	39.22 ± 65.05	99 (34)	21.33 [11.36; 31.29]	<b>&lt; 0.001</b>
M24	52.06 ± 99.89	80 (27)	19.04 [6.39; 31.68]	<b>0.004</b>

*All 292 eyes were included when data were available, and all available paired data were analyzed for calculating the differences compared to baseline.*



**Figure 3.** Changes in mean LFM from baseline to M24.

- A. Overall changes
- B. Changes in idiopathic uveitis subgroup
- C. Changes in sarcoidosis/sarcoidosis-like disease subgroup
- D. Changes in Birdshot chorioretinopathy subgroup
- E. Changes in Behçet/Behçet-like disease subgroup
- F. Changes in JIA subgroup

### ***Vasculitis***

A few data were available about vasculitis but the overall rate gradually decreased with less than a quarter of the patients having a vasculitis at M24, compared to half of the patients at baseline (Table 7, Figure 4A).

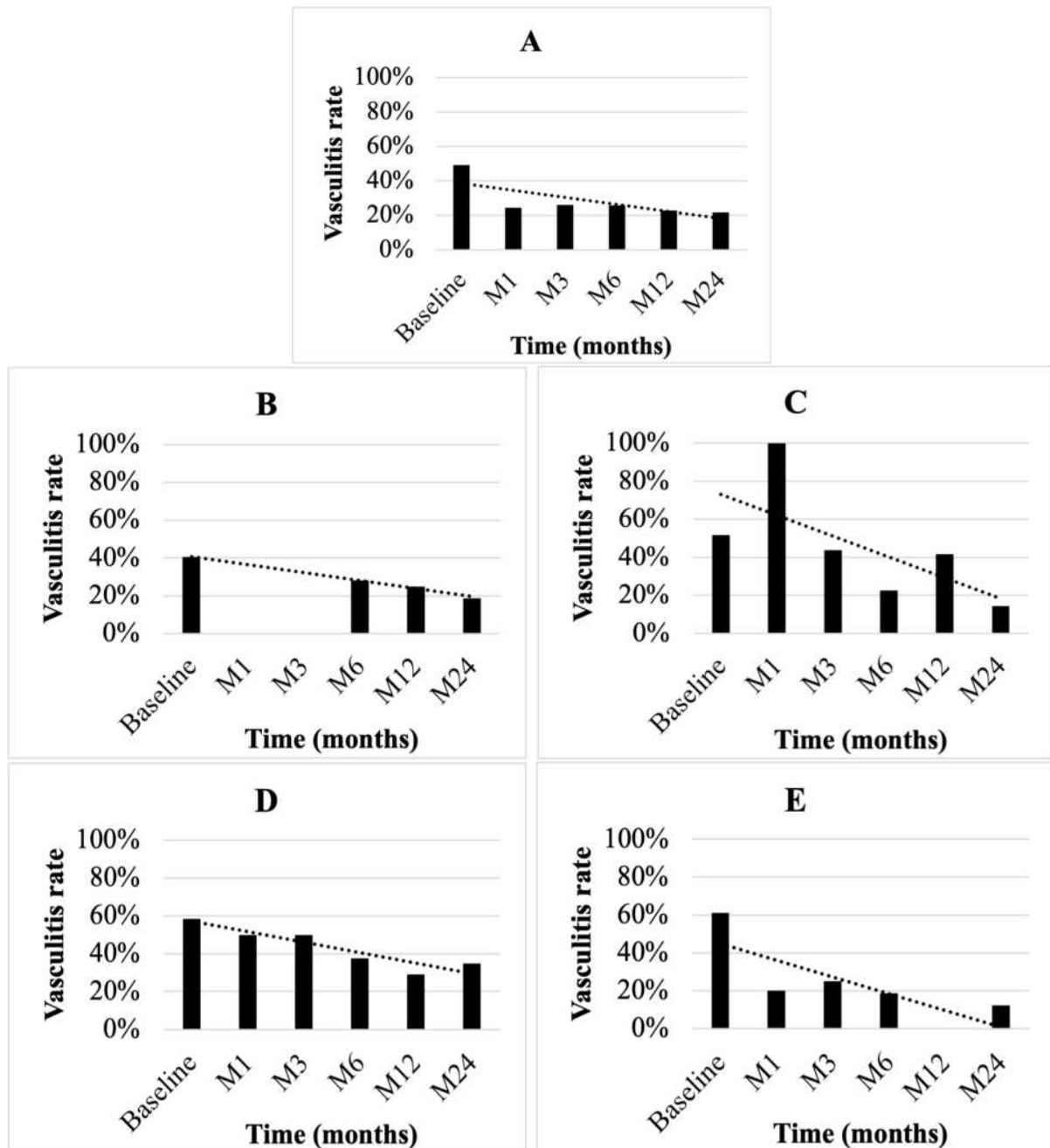


The improvement was clear in sarcoidosis/sarcoidosis-like subgroup (Figure 4C) and even more in Behçet/Behçet-like subgroup (Figure 4E).

**Table 7.** Changes in vasculitis rate from baseline to M24.

	Baseline	M1	M3	M6	M12	M24
Vasculitis rate, %	49	24	26	26	23	22
Available data, <i>n</i> (%)	138 (47)	37 (13)	69 (24)	101 (35)	88 (30)	78 (27)

All 292 eyes were included when data were available.



**Figure 4.** Changes in vasculitis rate from baseline to M24.

- A. Overall changes
- B. Changes in idiopathic uveitis subgroup
- C. Changes in sarcoidosis/sarcoidosis-like disease subgroup
- D. Changes in Birdshot chorioretinopathy subgroup
- E. Changes in Behçet/Behçet-like disease subgroup

### Visual field

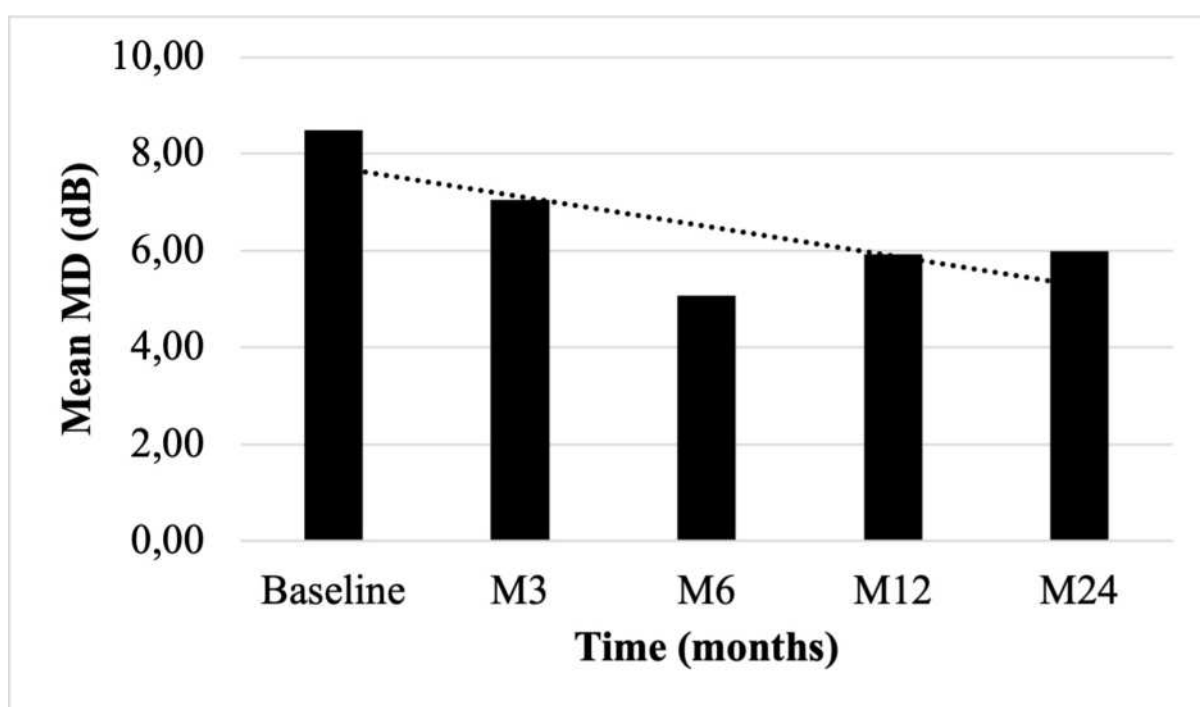
In patients with Birdshot chorioretinopathy, mean defect on the visual field reduced from 8.48 dB at baseline to 5.99 dB at M24 (Table 8, Figure 5).

**Table 8.** Changes in MD for patients with Birdshot chorioretinopathy from baseline to M24.

	Baseline	M1	M3	M6	M12	M24
MD (Mean Defect) in decibels, <i>mean ± SD</i>	8.48 ± 5.80	/	7.04 ± 5.81	5.07 ± 3.93	5.93 ± 6.35	5.99 ± 4.74
Available data, <i>n (%)</i>	26 (57)	4 (9)	26 (57)	16 (35)	32 (70)	24 (52)

*Mean MD and SD were not calculated at M1 because of the lack of data.*

*Available data are expressed as counts, and percentage of the eyes of patients having Birdshot chorioretinopathy (total = 46 eyes).*



**Figure 5.** Changes in MD for patients with Birdshot chorioretinopathy from baseline to M24.

### Recurrences

Eleven patients were treated for HLA-B27 associated uveitis, for a total of 13 anti-TNF therapies. Twenty-two recurrences occurred, i.e. an average of 1.7 recurrences per treatment. Patients were followed up for 40.1 patient-years meaning that there were about 0.5 recurrences per patient-year or 1 recurrence every 2 years.

### **Treatment duration**

Half of the patients stopped the treatment (Table 9) with a median treatment time of 24.5 months. The reason was exclusively a lack or loss of ocular efficacy in 13% of the cases (median treatment time: 12 months), remission in 11% (median treatment time: 29 months), and the occurrence of adverse events (AEs) in 9% (median treatment time: 21 months). In case of discontinuation for residual inflammation, a third of the patients were treated for JIA.

In case of discontinuation for remission (exclusively or partly), 30% of the patients had a relapse with a median onset time of 8 months. These patients relapsing were treated mainly for idiopathic uveitis (67%), with a median anti-TNF treatment time of 25.5 months. There was still corticotherapy for two of them (33%) with a median residual daily corticotherapy dose of 6 mg.

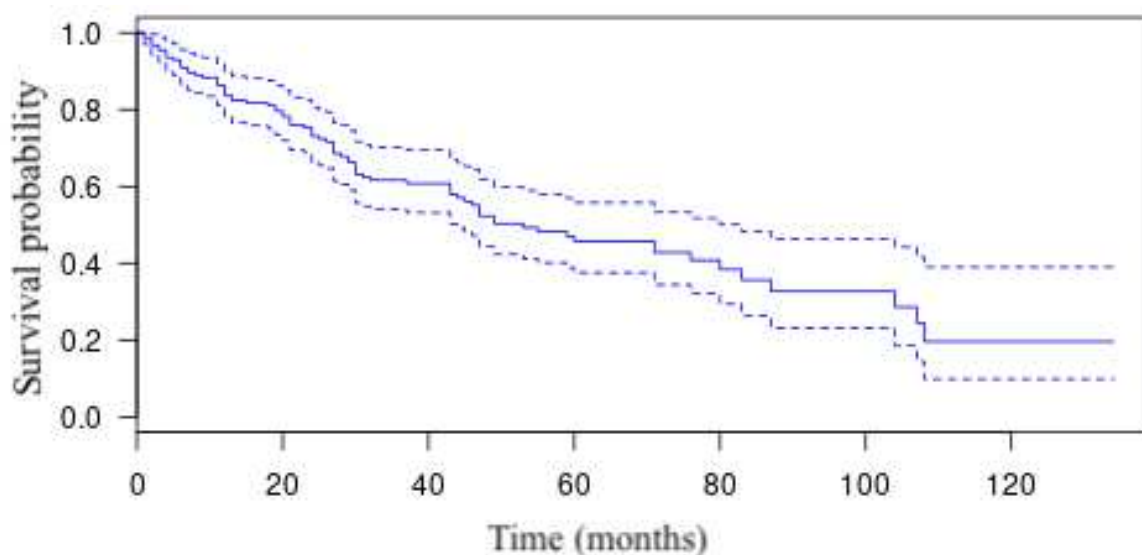
Figure 6 and Table 10 show the survival probability without discontinuing the treatment over time and the main reasons at several time points. The median survival time is about 50 months. Supplementary materials S8A to S8D detail the evolution in time of anti-TNF therapies discontinuation (Kaplan-Meier curves) according to the reason.

**Table 9.** Anti-TNF discontinuation.

	<b>Anti-TNF used (n = 160)</b>
<b>Anti-TNF therapy discontinuation, n (%)</b>	80 (50)
<b>Discontinuation reason, n (%)</b>	
<b>Lack/loss of ocular efficacy</b>	<b>21 (13)</b>
. Residual inflammation	8 (5)
. Residual ME	9 (6)
. Both	4 (3)
<b>Remission</b>	<b>17 (11)</b>
<b>AEs</b>	<b>15 (9)</b>
Self-medication/patient's choice	8 (5)
Lack/loss of extra-ocular efficacy	6 (4)
Pregnancy projects	2 (1)
Others <sup>1</sup>	11 (7)
<b>Treatment time in months in case of discontinuation of the treatment, median [min - max]</b>	24.5 [1 – 108]
In case of discontinuation for remission, exclusively or not:	
<b>Relapse, n (% of these patients)</b>	6 (30)
<b>Time to relapse in months, median [min - max]</b>	8 [3 – 23]

The three main discontinuation reasons are highlighted in bold.

<sup>1</sup>: including 2 patients with remission and pregnancy projects, 1 patient with remission and AEs, 2 patients with uncontrolled systemic disease associated with AEs, 1 patient who had no parenthood project anymore (switch back to methotrexate), 1 patient with lack of efficacy and uncontrolled systemic disease, 1 patient with lack of efficacy and AEs, 1 patient who had a chronic breakdown of the blood-retinal barrier without any modification of the LFM, 2 patients with safety concerns (stroke management and tuberculosis contact).



**Figure 6.** Kaplan-Meier curve of overall survival probability without discontinuing the treatment.

**Table 10.** Anti-TNF discontinuation over time.

Time-point	M6	M12	M24	M60	After
<b>Patients at risk (n = 155)</b>	<b>141</b>	<b>130</b>	<b>115</b>	<b>84</b>	<b>75</b>
<b>Discontinuation, n (%)</b>	<b>14 (9)</b>	<b>11 (7)</b>	<b>15 (10)</b>	<b>31 (20)</b>	<b>9 (6)</b>
Lack/loss of ocular efficacy	7 (5)	4 (3)	0 (0)	7 (5)	3 (2)
Remission	0 (0)	1 (1)	5 (3)	10 (6)	1 (1)
AEs	3 (2)	1 (1)	4 (3)	5 (3)	2 (1)
Self-medication/patient's choice	1 (1)	1 (1)	3 (2)	2 (1)	1 (1)
Lack/loss of extra-ocular efficacy	0 (0)	2 (1)	2 (1)	2 (1)	0 (0)
Pregnancy projects	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)
Others	3 (2)	2 (1)	0 (0)	4 (3)	2 (1)

*Five patients were lost to follow-up before any discontinuation of the treatment, so were excluded from this analysis (initial count of patients at risk: 155).*

*Every different anti-TNF therapy is defined as a "patient at risk", so patients who had 2 different anti-TNF therapies are considered twice.*

## Safety

Main reported AEs (Table 11) were pain (12%) at the injection site, myalgia or arthralgia, and cutaneous effects (18%). No allergic reactions were observed.

Serious infections remained rare (7%), mainly abscess. A few malignant lesions were reported too (2%), including one breast cancer, one high-grade serous carcinoma of the ovary, and one intraductal papillary mucinous neoplasm (IPMN) of the pancreas. Four demyelination cases (3%) were reported.

Only 19 anti-TNF therapies (12%) had to be discontinued partly or exclusively due to AEs: 6 because of various AEs (asthenia, insomnia, digestive disorders...), 5 because of disabling cutaneous effects (especially psoriasiform reaction, cracked skin on hands and feet, hypodermitis), 2 because of malignancy, 3 because of demyelination, 2 because of serious infections, and 1 because of malignancy and demyelination.

**Table 11.** AEs occurrence.

	<b>Anti-TNF used (n = 160)</b>
<b>Injection site pain, n (%)</b>	7 (4)
<b>Another pain (myalgia, arthralgia...), n (%)</b>	12 (8)
<b>Serious infections, n (%)</b>	11 (7)
Abscess	6 (4)
Urinary tract infection	2 (1)
Active tuberculosis	1 (1)
Others <sup>1</sup>	2 (1)
<b>Malignancy<sup>2</sup>, n (%)</b>	3 (2)
<b>Cutaneous effects, n (%)</b>	29 (18)
Hot flashes, sweats	10 (6)
Paradoxical psoriasiform reaction	5 (3)
Injection site reaction	4 (3)
Eczematiform reaction	3 (2)
Warts, verrucas	2 (1)
Inflammatory reaction <sup>3</sup>	2 (1)
Others (cracked skin...)	3 (2)
<b>Demyelination, n (%)</b>	4 (3)
<b>Others, n (%)</b>	24 (15)
Asthenia	7 (4)
Hair loss	3 (2)
Insomnia	6 (4)
Digestive disorders (nausea, stomach heaviness...)	6 (4)
Others (mood disorder, cough...)	2 (1)

<sup>1</sup>: others include a septic arthritis and a mediastinal lymphadenopathy.

<sup>2</sup>: including one breast cancer, one high-grade serous carcinoma of the ovary, and one intraductal papillary mucinous neoplasm (IPMN) of the pancreas.

<sup>3</sup>: including lichen planus and granulomatous hypodermitis.

## DISCUSSION

In this monocentric retrospective study, we showed real-world efficacy and safety of anti-TNF therapies in treating chronic NIU. This was consistent with clinical trials, and some other observational studies with fewer patients (46).

Indication of anti-TNF therapy was firstly inflammation only (56%), or with ME (29%). ME alone represented only 8% of the indications, maybe because local treatments can be used especially in case of asymmetrical ME (47,48). That also explains why 83% of cases were bilateral. Results were the same excluding anterior uveitis (52% of inflammation, 33% of inflammation with ME, 9% of ME only). Etiologies were similar to the main studies such as VISUAL I and II (49), except much less Vogt-Koyanagi-Harada disease (only 2 patients in our study, so 3% of panuveitis), which is consistent with some French studies (50). Especially there were as much idiopathic uveitis (30%) as in adalimumab groups of VISUAL I (33%) and II (25%) trials.

Anti-TNF were mainly a second-line corticosteroid-sparing therapy (54%) after methotrexate (46% of first-line). Although methotrexate is also the main first-line corticosteroid-sparing therapy in literature (51), the use of anti-TNF as soon as the second-line is relatively new (52).

Adalimumab was the main anti-TNF therapy used (90%), Humira® representing 70% of prescriptions; but more and more biosimilars are being used, as they were demonstrated as effective for much less cost (38,53). Few patients were treated with infliximab (4%), certolizumab (3%) and golimumab (3%), maybe because of the lack of authorization to date. It should be noted that the choice of the treatment depends on many other criteria: for example, before 2018 Humira® injections were containing citrate which made the injections painful; it can also be a practicality reason, some prefilled syringes being hard to manipulate; or safety reasons, for example certolizumab being not transferred across the placenta (54,55).

Anti-TNF therapies allowed an important corticosteroid sparing, with a median daily dose decreased from 10 mg at baseline to 5 mg at the last known visit in case of residual corticotherapy. The tapering was below 7 mg a day for 80% of the patients and 53% of the patients could even stop it.

Anti-TNF were significantly effective in reducing CMT, from M1 onward with a peak at M6. However, 28% of the patients needed adjuvant local corticotherapy in the evolution, a little less than the 40% of the MUST study (48). Few randomized controlled trials (26,28,56) and retrospective studies give us data about CMT decrease to date, with same results showing efficacy from 2 to 3 months and a maximal effect around 6 months (57,58). Results are even better when the initial indication of the anti-TNF therapy is macular edema (supplementary material S7): the mean CMT is decreased at M24 by 22% compared to baseline, with a mean CMT difference reaching 89  $\mu\text{m}$  (versus respectively 13% and 45  $\mu\text{m}$  overall).

This does tally with the improvement of VA from baseline to M24 but significantly from M6 only. LFM also significantly improved from M1 with important fluctuations according to the subgroup, partly because of patients having chronic blood-retinal barrier breakdown. The vasculitis rate, of course, also decreased, especially in Behçet's disease subgroup, which was already known (59,60) and explains the indication of this treatment in severe retinal vasculitis (17).

Our data have to be interpreted carefully as almost half the patients had at least one treatment associated, mainly methotrexate. Anyway, supplementary material S9 shows that there was no great difference according to additional treatment in reducing CMT.

Regarding subgroups, anti-TNF reaffirm their efficacy whatever the etiology. It was already suggested in refractory Birdshot chorioretinopathy (61,62) even if visual field data were lacking – however, complete remission with anti-TNF therapies alone can be challenging. Regardless of the use of adalimumab or infliximab, the efficacy was known in Behçet's disease too, maybe a little bit better with adalimumab (37,63). In HLA-B27 associated uveitis also, anti-TNF decrease the number of recurrences with 1 relapse every 2 years, which is less than with anti-IL17 treatments (64). In sarcoidosis as well (65), anti-TNF therapies can be used in case of uveitis refractory to conventional immunosuppressants. In childhood refractory chronic uveitis, some studies (66) suggested that adalimumab could better prevent flare recurrences than infliximab.

We found that half of the patients discontinued the treatment, because exclusively of lack or loss of ocular efficacy (13%), remission (11%), or occurrence of AEs (9%). Our results are in line with the literature, in the middle of BioÚvea Study Group's study (67) and VISUAL III (28) results: discontinuation of the treatment because of lack or loss of efficacy respectively in 19% and 8%, because of AEs respectively in 9% and 18%.

Median treatment time was 12 months in case of lack or loss of ocular efficacy, 21 months in case of AEs, and up to 29 months in case of remission; in line with BioÚvea Study Group's study (67) that found respectively 19 months, 18 months, and 28 months.

70% of the patients that stopped the treatment for remission did not present any relapse, and those who relapsed did so with a median onset time of 8 months.

Quality of life was not assessed, but these treatments are really helpful for patients who express their satisfaction daily, as much as saying for some of them that they get a new lease of life. Practicality of use is particularly pointed out with easy subcutaneous injections.

Our study didn't reveal any new AE. It was first mild AEs that did not require discontinuation of the treatment: pain (12%) at the injection site or myalgia or arthralgia, and cutaneous effects (18%). These are well known to date (68,69), even if they are often temporary, with imputability concerns (cutaneous lesions due to corticotherapy, psoriasiform lesions due to HLA-B27 associated disease...).

Serious infections remained rare (7%), represented mainly by abscess also with imputability concerns (concomitant intake of non-steroidal anti-inflammatory drug (NSAID) for example). However, it involves ruling out any infection during the follow-up, to check vaccinations and rule out any latent tuberculosis infection (70) before the beginning of the treatment. Indeed, one patient needed hospitalization in intensive care unit for tuberculosis miliary despite a pre-therapeutic negative QuantiFERON® test; reminding us that in case of equivocal or even negative results in a context of severely depressed cell-mediated immunity (as here because of MMF), this test may be repeated (71,72) or even considered positive.

We noticed some paradoxical reactions (73), which means pathological conditions that usually respond to this treatment (including psoriasis, granulomatous diseases...). On the contrary of some studies (74,75) we found few autoimmune diseases, in particular neither vasculitis nor lupus. The demyelination risk (3%), involves checking a brain MRI before beginning an anti-TNF therapy for non-anterior uveitis (17,76).

Few malignant lesions were reported (2%). The literature contains conflicting results about this subject: a few studies showed an increased risk of cancers, especially skin cancers (77,78), but a majority did not, even with long-term treatments for rheumatologic or digestive diseases (79–81). Consequently, it is important to inform all patients of the necessary precautions (sun protection, etc.) and to carry out regular screening (including annual dermatological monitoring).

No allergic reactions were noticed.



The main strength of our study is its number of patients much more important than in previous retrospective studies, with a standardized uniform follow up in multidisciplinary consultations for most of them. It brings some results consistent with literature, it specifies the CMT evolution in subgroups. Similarly, visual field evolution is, to the best of our knowledge, quite a new element.

However, we acknowledge some limitations. Data were retrospectively collected, so the results must be interpreted with caution. Even though the study size was substantial as said above, it was still not enough to deal with other treatments than adalimumab in depth, and we could not suggest predictive factors in response to anti-TNF. Some studies suggest that the use of adalimumab rather than infliximab, and concomitant inactive systemic disease would be associated with a lower risk of treatment failure (82).

Furthermore, we did hardly ever assess serum adalimumab and antibodies against adalimumab (AAA) levels, nor other antibodies levels, whereas it has been shown that AAA were associated with undetectable adalimumab levels and worse uveitis outcomes (83). AAA are rare in some studies with rates between 2.7% and 4.8% but sometimes up to 35% (26,84). It may depend on the treatment duration, that is much shorter than for rheumatologic or digestive diseases. Anyway, a low level of AAA can have no consequences (85), so the interpretation of their presence is sometimes complicated.

This study gives us some clues about the delay before discontinuation of the treatment that we need to confirm with more studies, some of which being underway (86). Similarly, some studies have been carried out on the cost of the treatments (87,88) (which varies between 10,000 and 15,000€ per year), an important criterion to consider in these times of health-care crisis; but further studies are needed on predictive criteria or biomarkers for response as in other diseases (89,90), in order to avoid expensive and unnecessary treatments, and to evaluate costs from a societal perspective (savings in terms of work stoppages or quality of life).

In case of refractory ME, it is possible to use Interferon (91–93) or Tocilizumab (94–98), Tocilizumab improving the response of uveitic ME compared to anti-TNF (97,98).

To conclude, this study showed real-life efficacy and safety of anti-TNF. Their use is already recommended in second-line in case of corticoresistance or in third-line in case of corticodépendance after the use of immunomodulators, and it could be an alternative as a second-line therapy especially in case of severe inflammation or important ME.

## BIBLIOGRAPHY

1. Standardization of Uveitis Nomenclature for Reporting Clinical Data. Results of the First International Workshop. *Am J Ophthalmol.* 2005 Sep;140(3):509–16.
2. Touhami S, Audo I, Terrada C, Gaudric A, LeHoang P, Touitou V, et al. Neoplasia and intraocular inflammation: From masquerade syndromes to immunotherapy-induced uveitis. *Progress in Retinal and Eye Research.* 2019 Sep 1;72:100761.
3. Sève P, Kodjikian L, Adélaïde L, Jamilloux Y. Uveitis in adults: What do rheumatologists need to know? *Joint Bone Spine.* 2015 Oct;82(5):308–14.
4. Joltikov KA, Lobo-Chan AM. Epidemiology and Risk Factors in Non-infectious Uveitis: A Systematic Review. *Front Med (Lausanne).* 2021 Sep 10;8:695904.
5. Thorne JE, Suhler E, Skup M, Tari S, Macaulay D, Chao J, et al. Prevalence of Noninfectious Uveitis in the United States: A Claims-Based Analysis. *JAMA Ophthalmol.* 2016 Nov 1;134(11):1237–45.
6. Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study. *Ophthalmology.* 2004 Mar;111(3):491–500; discussion 500.
7. Bajwa A, Osmanzada D, Osmanzada S, Khan I, Patrie J, Xin W, et al. Epidemiology of uveitis in the mid-Atlantic United States. *Clin Ophthalmol.* 2015;9:889–901.
8. Lardenoye CWTA, van Kooij B, Rothova A. Impact of macular edema on visual acuity in uveitis. *Ophthalmology.* 2006 Aug;113(8):1446–9.
9. Accorinti M, Okada AA, Smith JR, Gilardi M. Epidemiology of Macular Edema in Uveitis. *Ocul Immunol Inflamm.* 2019;27(2):169–80.
10. Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P, Murray PI. Degree, duration, and causes of visual loss in uveitis. *Br J Ophthalmol.* 2004 Sep;88(9):1159–62.
11. Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. *Br J Ophthalmol.* 1996;80(9):844–848.
12. Schiffman RM, Jacobsen G, Whitcup SM. Visual functioning and general health status in patients with uveitis. *Arch Ophthalmol.* 2001 Jun;119(6):841–9.
13. Albin TA, Rice JB, White AG, Johnson M, Reiff J, Lima AF, et al. Economic Burden of Non-Infectious Inflammatory Eye Disease (NIIED) in a Commercially-Insured Population in the United States. *Ocul Immunol Inflamm.* 2020;28(1):164–74.
14. Srivastava SK, Ramana KV. Focus on molecules: nuclear factor-kappaB. *Exp Eye Res.* 2009 Jan;88(1):2–3.
15. Fardeau C, Champion E, Massamba N, LeHoang P. Uveitic macular edema. *Eye (Lond).* 2016 Oct;30(10):1277–92.
16. Massa H, Pipis SY, Adewoyin T, Vergados A, Patra S, Panos GD. Macular edema associated with non-infectious uveitis: pathophysiology, etiology, prevalence, impact and management challenges. *Clin Ophthalmol.* 2019;13:1761–77.

17. Quartier-Dit-Maire P, Saadoun D, Belot A, Kaplanski G, Kodjikian L, Kone-Paut I, et al. Protocole National de Diagnostic et de soins sur les Uvéites Chroniques Non Infectieuses de l'enfant et de l'adulte. 2020.
18. HUMIRA® (adalimumab) injection, for subcutaneous use. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/125057s410lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125057s410lbl.pdf)
19. CT-15576\_HUMIRA\_PIC\_EI\_uveite\_Avis2\_CT15576.pdf [Internet]. Available from: [https://www.has-sante.fr/upload/docs/evamed/CT-15576\\_HUMIRA\\_PIC\\_EI\\_uveite\\_Avis2\\_CT15576.pdf](https://www.has-sante.fr/upload/docs/evamed/CT-15576_HUMIRA_PIC_EI_uveite_Avis2_CT15576.pdf)
20. Kalliolias GD, Ivashkiv LB. TNF biology, pathogenic mechanisms and emerging therapeutic strategies. *Nat Rev Rheumatol*. 2016 Jan;12(1):49–62.
21. Yang S, Wang J, Brand DD, Zheng SG. Role of TNF-TNF Receptor 2 Signal in Regulatory T Cells and Its Therapeutic Implications. *Front Immunol*. 2018;9:784.
22. Gerriets V, Goyal A, Khaddour K. Tumor Necrosis Factor Inhibitors. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK482425/>
23. Shi JH, Sun SC. Tumor Necrosis Factor Receptor-Associated Factor Regulation of Nuclear Factor  $\kappa$ B and Mitogen-Activated Protein Kinase Pathways. *Front Immunol*. 2018 Aug 9;9:1849.
24. Nesbitt A, Fossati G, Bergin M, Stephens P, Stephens S, Foulkes R, et al. Mechanism of action of certolizumab pegol (CDP870): in vitro comparison with other anti-tumor necrosis factor alpha agents. *Inflamm Bowel Dis*. 2007 Nov;13(11):1323–32.
25. Ellis CR, Azmat CE. Adalimumab. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK557889/>
26. Jaffe GJ, Dick AD, Brézin AP, Nguyen QD, Thorne JE, Kestelyn P, et al. Adalimumab in Patients with Active Noninfectious Uveitis. *N Engl J Med*. 2016 Sep 8;375(10):932–43.
27. Nguyen QD, Merrill PT, Jaffe GJ, Dick AD, Kurup SK, Sheppard J, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet*. 2016 Sep 17;388(10050):1183–92.
28. Suhler EB, Jaffe GJ, Fortin E, Lim LL, Merrill PT, Dick AD, et al. Long-Term Safety and Efficacy of Adalimumab in Patients with Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis. *Ophthalmology*. 2021 Jun 1;128(6):899–909.
29. Quartier P, Baptiste A, Despert V, Allain-Launay E, Koné-Paut I, Belot A, et al. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. *Ann Rheum Dis*. 2018 Jul;77(7):1003–11.

30. Ramanan AV, Dick AD, Benton D, Compeyrot-Lacassagne S, Dawoud D, Hardwick B, et al. A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial). *Trials*. 9 jan 2014;15(1). Available from: <https://doi.org/10.1186/1745-6215-15-14>
31. anx\_154189\_fr.pdf [Internet]. Available from: [https://ec.europa.eu/health/documents/community-register/2021/20211216154189/anx\\_154189\\_fr.pdf](https://ec.europa.eu/health/documents/community-register/2021/20211216154189/anx_154189_fr.pdf)
32. Davies R, De Cock D, Kearsley-Fleet L, Southwood T, Baildam E, Beresford MW, et al. The risk of uveitis in patients with JIA receiving etanercept: the challenges of analysing real-world data. *Rheumatology (Oxford)*. 2020 Jun 1;59(6):1391–7.
33. Brito-Zerón P, Perez-Alvarez R, Ramos-Casals M. Etanercept and uveitis: friends or foes? *Current Medical Research and Opinion*. 2015 Feb 1;31(2):251–2.
34. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. *Arthritis Rheum*. 2007 Oct;56(10):3248–52.
35. Suhler EB, Smith JR, Giles TR, Lauer AK, Wertheim MS, Kurz DE, et al. Infliximab therapy for refractory uveitis: 2-year results of a prospective trial. *Arch Ophthalmol*. 2009 Jun;127(6):819–22.
36. Vallet H, Seve P, Biard L, Baptiste Fraison J, Bielefeld P, Perard L, et al. Infliximab Versus Adalimumab in the Treatment of Refractory Inflammatory Uveitis: A Multicenter Study From the French Uveitis Network. *Arthritis Rheumatol*. 2016 Jun;68(6):1522–30.
37. Atienza-Mateo B, Martín-Varillas JL, Calvo-Río V, Demetrio-Pablo R, Beltrán E, Sánchez-Bursón J, et al. Comparative Study of Infliximab Versus Adalimumab in Refractory Uveitis due to Behçet’s Disease: National Multicenter Study of 177 Cases. *Arthritis Rheumatol*. 2019 Dec;71(12):2081–9.
38. Jourdain H, Hoisnard L, Sbidian E, Zureik M. TNF-alpha inhibitors biosimilar use in France: a nationwide population-based study using the French National Health Data System. *Sci Rep*. 2022 Nov 15;12(1):19569.
39. Hernanz I, Miguel Escuder L, Chamorro L, Moll-Udina A, Espinosa G, Sainz de la Maza M, et al. Tuberculosis-Related Uveitis in Patients under Anti-TNF-alpha Therapy: A Case Series. *Ocul Immunol Inflamm*. 2022 May 19;30(4):839–44.
40. Kemanetzoglou E, Andreadou E. CNS Demyelination with TNF- $\alpha$  Blockers. *Curr Neurol Neurosci Rep*. 2017 Apr;17(4):36.
41. Williams I, Uhlig HH. Demyelination After Anti-TNF Therapy: Who is at Risk? *Journal of Crohn’s and Colitis*. 2020 Dec 1;14(12):1651–2.
42. Gharib MH, AlKahlout MA, Garcia Canibano B, Theophiel Deleu D, Malallah AlEsa H, AlEmadi S. Demyelinating Neurological Adverse Events following the Use of Anti-TNF- $\alpha$  Agents: A Double-Edged Sword. *Case Rep Neurol Med*. 2022;2022:3784938.
43. tableau-2-correspondance-acuité.pdf [Internet]. Available from: <https://www.snof.org/sites/default/files/tableau-2-correspondance-acuit%C3%A9.pdf>

44. Holladay JT. Proper method for calculating average visual acuity. *J Refract Surg.* 1997;13(4):388–91.
45. BiostaTGV - Statistiques en ligne [Internet]. Available from: <https://biostatgv.sentiweb.fr/>
46. Ming S, Xie K, He H, Li Y, Lei B. Efficacy and safety of adalimumab in the treatment of non-infectious uveitis: a meta-analysis and systematic review. *Drug Des Devel Ther.* 2018;12:2005–16.
47. Thorne JE, Sugar EA, Holbrook JT, Burke AE, Altaweel MM, Vitale AT, et al. Periocular Triamcinolone vs. Intravitreal Triamcinolone vs. Intravitreal Dexamethasone Implant for the Treatment of Uveitic Macular Edema: The PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT) Trial. *Ophthalmology.* 2019 Feb;126(2):283–95.
48. Tomkins-Netzer O, Lightman SL, Burke AE, Sugar EA, Lim LL, Jaffe GJ, et al. Seven-Year Outcomes of Uveitic Macular Edema: The Multicenter Uveitis Steroid Treatment Trial and Follow-up Study Results. *Ophthalmology.* Sep 2020. Available from: <https://doi.org/10.1016/j.ophtha.2020.08.035>
49. Goto H, Zako M, Namba K, Hashida N, Kaburaki T, Miyazaki M, et al. Adalimumab in Active and Inactive, Non-Infectious Uveitis: Global Results from the VISUAL I and VISUAL II Trials. *Ocul Immunol Inflamm.* 2019;27(1):40–50.
50. Bodaghi B, Cassoux N, Wechsler B, Hannouche D, Fardeau C, Papo T, et al. Chronic severe uveitis: etiology and visual outcome in 927 patients from a single center. *Medicine (Baltimore).* 2001 Jul;80(4):263–70.
51. Kaplan-Messas A, Barkana Y, Avni I, Neumann R. Methotrexate as a first-line corticosteroid-sparing therapy in a cohort of uveitis and scleritis. *Ocular Immunology and Inflammation.* 2003 Jan 1;11(2):131–9.
52. Corticosteroid-sparing therapy: practice patterns among uveitis specialists | SpringerLink [Internet]. Available from: <https://link.springer.com/article/10.1007/s12348-011-0047-5>
53. Fabiani C, Vitale A, Emmi G, Sgheri A, Lopalco G, Sota J, et al. The Role of Biosimilars in Uveitis: Long-Term Real-World Outcomes of the Switch From Original to Biosimilar TNF-Alpha Inhibitors. *Front Pharmacol.* 9 déc 2019;10. Available from: <https://doi.org/10.3389/fphar.2019.01468>
54. Nielsen OH, Loftus Jr EV, Jess T. Safety of TNF- $\alpha$  inhibitors during IBD pregnancy: a systematic review. *BMC Medicine.* 2013 Jul 31;11(1):174.
55. Beghin D. [Placental transfer of monoclonal antibodies: The example of anti-TNF alpha drugs]. *Gynecol Obstet Fertil Senol.* 2021 Sep;49(9):724–6.
56. Barry RJ, Tallouzi MO, Bucknall N, Mathers JM, Murray PI, Calvert MJ, et al. Anti-tumour necrosis factor biological therapies for the treatment of uveitic macular oedema (UMO) for non-infectious uveitis. *Cochrane Database Syst Rev.* 2018 Dec 18;12:CD012577.
57. Schaap-Fogler M, Amer R, Friling R, Priel E, Kramer M. Anti-TNF- $\alpha$  agents for refractory cystoid macular edema associated with noninfectious uveitis. *Graefes Arch Clin Exp Ophthalmol.* 2014 Apr;252(4):633–40.

58. Markomichelakis NN, Theodossiadis PG, Pantelia E, Papaefthimiou S, Theodossiadis GP, Sfikakis PP. Infliximab for chronic cystoid macular edema associated with uveitis. *Am J Ophthalmol*. 2004 Oct;138(4):648–50.
59. Yang S, Huang Z, Hu Y, Zhang J, Liu X, Li H, et al. The Efficacy of Adalimumab as an Initial Treatment in Patients with Behçet’s Retinal Vasculitis. *Frontiers in Pharmacology* [Internet]. 2021;12. Available from: <https://www.frontiersin.org/articles/10.3389/fphar.2021.609148>
60. Fabiani C, Sota J, Rigante D, Vitale A, Emmi G, Lopalco G, et al. Efficacy of adalimumab and infliximab in recalcitrant retinal vasculitis inadequately responsive to other immunomodulatory therapies. *Clin Rheumatol*. 2018 Oct;37(10):2805–9.
61. Artornsombudh P, Gevorgyan O, Payal A, Siddique SS, Foster CS. Infliximab treatment of patients with birdshot retinochoroidopathy. *Ophthalmology*. 2013 Mar;120(3):588–92.
62. Huis Het Veld PI, van Asten F, Kuijpers RWAM, Rothova A, de Jong EK, Hoyng CB. ADALIMUMAB THERAPY FOR REFRACTORY BIRDSHOT CHORIORETINOPATHY. *Retina*. 2019 Nov;39(11):2189–97.
63. Vallet H, Riviere S, Sanna A, Deroux A, Moulis G, Addimanda O, et al. Efficacy of anti-TNF alpha in severe and/or refractory Behçet’s disease: Multicenter study of 124 patients. *J Autoimmun*. 2015 Aug;62:67–74.
64. Roche D, Badard M, Boyer L, Lafforgue P, Pham T. Incidence of anterior uveitis in patients with axial spondyloarthritis treated with anti-TNF or anti-IL17A: a systematic review, a pairwise and network meta-analysis of randomized controlled trials. *Arthritis Res Ther*. 2021 Jul 16;23(1):192.
65. Riancho-Zarrabeitia L, Calvo-Río V, Blanco R, Mesquida M, Adan AM, Herreras JM, et al. Anti-TNF- $\alpha$  therapy in refractory uveitis associated with sarcoidosis: Multicenter study of 17 patients. *Seminars in Arthritis and Rheumatism*. 2015 Dec 1;45(3):361–8.
66. Simonini G, Taddio A, Cattalini M, Caputo R, De Libero C, Naviglio S, et al. Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. *Arthritis Care Res (Hoboken)*. 2011 Apr;63(4):612–8.
67. Llorenç V, Cordero-Coma M, Blanco-Esteban A, Heras-Mulero H, Losada-Castillo MJ, Jovani-Casano V, et al. Drug Retention Rate and Causes of Discontinuation of Adalimumab in Uveitis: Real-World Data from the Biotherapies in Uveitis (BioÚvea) Study Group. *Ophthalmology*. 2020 Jun;127(6):814–25.
68. Vorčáková K, Péčová T, Martinásková K, Nováčeková K, Péč J, Vorčáková K, et al. Skin Adverse Reactions Related to TNF Alpha Inhibitors: Classification and Therapeutic Approach in Psoriatic Patients. In: *Tailored Treatments in Psoriatic Patients* [Internet]. IntechOpen; 2019. Available from: <https://www.intechopen.com/chapters/66225>
69. Mocchi G, Marzo M, Papa A, Armuzzi A, Guidi L. Dermatological adverse reactions during anti-TNF treatments: focus on inflammatory bowel disease. *J Crohns Colitis*. 2013 Nov;7(10):769–79.

70. Seyhoglu E, Uyaroglu OA, Erden A, Kilic L, Karadag O, Akdogan A, et al. QuantiFERON®-TB Gold In-Tube test can be used for screening latent tuberculosis before biological treatment in a Bacille Calmette-Guérin (BCG)-vaccinated country: the HUR-BIO single-center real-life results. *Clin Rheumatol*. 2021 May;40(5):2027–35.
71. Komukai J, Matsumoto K, Hirota S, Yoshida H, Koda S, Terakawa K, et al. [Interpreting ‘equivocal’ results obtained from the QuantiFERON-TB Gold In-Tube test in contact investigations]. *Kekkaku*. 2013 Mar;88(3):301–4.
72. Brown J, Kumar K, Reading J, Harvey J, Murthy S, Capocci S, et al. Frequency and significance of indeterminate and borderline Quantiferon Gold TB IGRA results. *Eur Respir J*. 2017 Oct;50(4):1701267.
73. Review: Paradoxical reactions under TNF- $\alpha$  blocking agents and other biological agents given for chronic immune-mediated diseases: an analytical and comprehensive overview - PMC [Internet]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4964220/>
74. Ramos-Casals M, Brito-Zerón P, Muñoz S, Soria N, Galiana D, Bertolaccini L, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine (Baltimore)*. 2007 Jul;86(4):242–51.
75. Lopetuso LR, Cuomo C, Mignini I, Gasbarrini A, Papa A. Focus on Anti-Tumour Necrosis Factor (TNF)- $\alpha$ -Related Autoimmune Diseases. *Int J Mol Sci*. 2023 May 3;24(9):8187.
76. Kunchok A, Aksamit AJ Jr, Davis JM III, Kantarci OH, Keegan BM, Pittock SJ, et al. Association Between Tumor Necrosis Factor Inhibitor Exposure and Inflammatory Central Nervous System Events. *JAMA Neurology*. 2020 Aug 1;77(8):937–46.
77. Adalsteinsson JA, Muzumdar S, Waldman R, Hu C, Wu R, Ratner D, et al. Anti-tumor necrosis factor therapy is associated with increased in situ squamous cell carcinoma of the skin: A population-based case-control study. *J Am Acad Dermatol*. 2021 Jun;84(6):1760–2.
78. Calip GS, Patel PR, Adimadhyam S, Xing S, Wu Z, Sweiss K, et al. Tumor necrosis factor-alpha inhibitors and risk of non-Hodgkin lymphoma in a cohort of adults with rheumatologic conditions. *Int J Cancer*. 2018 Sep 1;143(5):1062–71.
79. Burmester GR, Mease P, Dijkmans B a. C, Gordon K, Lovell D, Panaccione R, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. *Ann Rheum Dis*. 2009 Dec;68(12):1863–9.
80. Muller M, D’Amico F, Bonovas S, Danese S, Peyrin-Biroulet L. TNF Inhibitors and Risk of Malignancy in Patients with Inflammatory Bowel Diseases: A Systematic Review. *J Crohns Colitis*. 2021 May 4;15(5):840–59.
81. Mercer LK, Lunt M, Low ALS, Dixon WG, Watson KD, Symmons DPM, et al. Risk of solid cancer in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis*. 2015 Jun;74(6):1087–93.

82. Al-Janabi A, El Nokrashy A, Sharief L, Nagendran V, Lightman S, Tomkins-Netzer O. Long-Term Outcomes of Treatment with Biological Agents in Eyes with Refractory, Active, Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis. *Ophthalmology*. 2020 Mar;127(3):410–6.
83. Cordero-Coma M, Calleja-Antolín S, Garzo-García I, Nuñez-Garnés AM, Álvarez-Castro C, Franco-Benito M, et al. Adalimumab for Treatment of Noninfectious Uveitis: Immunogenicity and Clinical Relevance of Measuring Serum Drug Levels and Antidrug Antibodies. *Ophthalmology*. 2016 Dec;123(12):2618–25.
84. Bellur S, McHarg M, Kongwattananon W, Vitale S, Sen HN, Kodati S. Antidrug Antibodies to Tumor Necrosis Factor  $\alpha$  Inhibitors in Patients With Noninfectious Uveitis. *JAMA Ophthalmology*. 2023 Feb 1;141(2):150–6.
85. Leinonen ST, Aalto K, Kotaniemi KM, Kivelä TT. Anti-adalimumab antibodies in juvenile idiopathic arthritis-related uveitis. *Clin Exp Rheumatol*. 2017;35(6):1043–6.
86. Adalimumab in JIA-associated Uveitis Stopping Trial - Full Text View - ClinicalTrials.gov [Internet]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03816397>
87. Fragoulakis V, Vitsou E, Hernandez AC, Maniatakis N. Economic evaluation of anti-TNF agents for patients with rheumatoid arthritis in Greece. *CEOR*. 2015 Jan 16;7:85–93.
88. Schabert VF, Watson C, Gandra SR, Goodman S, Fox KM, Harrison DJ. Annual costs of tumor necrosis factor inhibitors using real-world data in a commercially insured population in the United States. *J Med Econ*. 2012;15(2):264–75.
89. Bergman MJ, Kivitz AJ, Pappas DA, Kremer JM, Zhang L, Jeter A, et al. Clinical Utility and Cost Savings in Predicting Inadequate Response to Anti-TNF Therapies in Rheumatoid Arthritis. *Rheumatol Ther*. 2020 Dec 1;7(4):775–92.
90. Leone GM, Mangano K, Petralia MC, Nicoletti F, Fagone P. Past, Present and (Foreseeable) Future of Biological Anti-TNF Alpha Therapy. *J Clin Med*. 2023 Feb 17;12(4):1630.
91. Deuter CME, Fausel J, Doycheva D, Zierhut M. Long-term results of therapy with interferon alpha in chronic uveitic macular edema. *Investigative Ophthalmology & Visual Science*. 2019 Jul 22;60(9):3515.
92. Couret C, Servant M, Lebranchu P, Hamidou M, Weber M. Efficacy and Safety of Interferon Alpha 2A and Pegylated Interferon Alpha 2A in Inflammatory Macular Edema. *Ocul Immunol Inflamm*. 2020;28(2):329–36.
93. De Simone L, Gentile P, Aldigeri R, Mastrofilippo V, Bolletta E, Gozzi F, et al. Effectiveness of Pegylated Interferon Alpha-2a in Post-Uveitic Macular Edema Previously Responding to Non-Pegylated Interferon. *Ocul Immunol Inflamm*. 2023 Apr 24;1–5.
94. Adán A, Mesquida M, Llorenç V, Espinosa G, Molins B, Hernández MV, et al. Tocilizumab treatment for refractory uveitis-related cystoid macular edema. *Graefes Arch Clin Exp Ophthalmol*. 2013 Nov;251(11):2627–32.



95. Mesquida M, Molins B, Llorenç V, Sainz de la Maza M, Adán A. Long-term effects of tocilizumab therapy for refractory uveitis-related macular edema. *Ophthalmology*. 2014 Dec;121(12):2380–6.
96. Vegas-Revenga N, Calvo-Río V, Mesquida M, Adán A, Hernández MV, Beltrán E, et al. Anti-IL6-Receptor Tocilizumab in Refractory and Noninfectious Uveitic Cystoid Macular Edema: Multicenter Study of 25 Patients. *Am J Ophthalmol*. 2019 Apr;200:85–94.
97. Leclercq M, Andrillon A, Maalouf G, Sève P, Bielefeld P, Gueudry J, et al. Anti-Tumor Necrosis Factor  $\alpha$  versus Tocilizumab in the Treatment of Refractory Uveitic Macular Edema: A Multicenter Study from the French Uveitis Network. *Ophthalmology*. 2022 May;129(5):520–9.
98. Barroso-García N, Atienza-Mateo B, Ferraz-Amaro I, Prieto-Peña D, Beltrán E, Adán A, et al. Anti-TNF vs tocilizumab in refractory uveitic cystoid macular edema due to Behcet's disease. Multicenter study of 49 patients. *Semin Arthritis Rheum*. 2023 Feb;58:152153.

## SUPPLEMENTARY MATERIALS

### Supplementary material S1.

Classification and description of uveitis according to the SUN (standardization of uveitis nomenclature) working group.

Adapted from: Standardization of Uveitis Nomenclature for Reporting Clinical Data. Results of the First International Workshop. Am J Ophthalmol. sept 2005;140(3):509-16.

**S1A.** The SUN working group anatomical classification of uveitis.

Type		Primary clinical inflammation site	Includes
Anterior uveitis	Panuveitis	Anterior chamber	Iritis, iridocyclitis, anterior cyclitis
Intermediate uveitis		Vitreous	Pars planitis, posterior cyclitis, hyalitis
Posterior uveitis		Retina or choroid	Focal/multifocal/diffuse choroiditis, chorioretinitis, retinochoroiditis, retinitis, neuroretinitis

**S1B.** The SUN working group descriptors of uveitis.

Onset	Duration	Course
- Sudden - Insidious	- Limited: duration $\leq$ 3 months - Persistent: duration $>$ 3 months	- Acute: episode of sudden onset and limited duration - Recurrent: repeated episodes separated by inactivity periods (without treatment) $\geq$ 3 months - Chronic: persistent uveitis with relapse in $<$ 3 months after discontinuing treatment

## Supplementary material S2.

Simplified summary of inflammatory pathways implicated with TNF $\alpha$ .

Personal work based on several references:

- Wajant H, Siegmund D. TNFR1 and TNFR2 in the Control of the Life and Death Balance of Macrophages. *Front Cell Dev Biol.* 2019;7:91. Published 2019 May 29. doi:10.3389/fcell.2019.00091
- Gough P, Myles IA. Tumor Necrosis Factor Receptors: Pleiotropic Signaling Complexes and Their Differential Effects. *Front Immunol.* 2020;11:585880. Published 2020 Nov 25. doi:10.3389/fimmu.2020.585880
- Liu, T., Zhang, L., Joo, D. et al. NF- $\kappa$ B signaling in inflammation. *Sig Transduct Target Ther* 2, 17023 (2017). <https://doi.org/10.1038/sigtrans.2017.23>
- Pannicke T, Uckermann O, Iandiev I, Wiedemann P, Reichenbach A, Bringmann A. Ocular inflammation alters swelling and membrane characteristics of rat Müller glial cells. *J Neuroimmunol.* 2005;161(1-2):145-154. doi:10.1016/j.jneuroim.2005.01.003
- Liu XQ, Kobayashi H, Jin ZB, Wada A, Nao-I N. Differential expression of Kir4.1 and aquaporin 4 in the retina from endotoxin-induced uveitis rat. *Mol Vis.* 2007;13:309-317. Published 2007 Mar 1.
- Luna JD, Chan CC, Derevjanić NL, et al. Blood-retinal barrier (BRB) breakdown in experimental autoimmune uveoretinitis: comparison with vascular endothelial growth factor, tumor necrosis factor alpha, and interleukin-1beta-mediated breakdown. *J Neurosci Res.* 1997;49(3):268-280. doi:10.1002/(sici)1097-4547(19970801)49:3<268::aid-jnr2>3.0.co;2-a
- Chin MS, Nagineni CN, Hooper LC, Detrick B, Hooks JJ. Cyclooxygenase-2 gene expression and regulation in human retinal pigment epithelial cells. *Invest Ophthalmol Vis Sci.* 2001;42(10):2338-2346.
- Zech JC, Pouvreau I, Cotinet A, Goureau O, Le Varlet B, de Kozak Y. Effect of cytokines and nitric oxide on tight junctions in cultured rat retinal pigment epithelium. *Invest Ophthalmol Vis Sci.* 1998;39(9):1600-1608.
- Peng S, Gan G, Rao VS, Adelman RA, Rizzolo LJ. Effects of proinflammatory cytokines on the claudin-19 rich tight junctions of human retinal pigment epithelium. *Invest Ophthalmol Vis Sci.* 2012;53(8):5016-5028. Published 2012 Jul 27. doi:10.1167/iovs.11-8311
- Harada C, Mitamura Y, Harada T. The role of cytokines and trophic factors in epiretinal membranes: involvement of signal transduction in glial cells. *Prog Retin Eye Res.* 2006;25(2):149-164. doi:10.1016/j.preteyeres.2005.09.001

### Abbreviations:

*AQP4 channels: aquaporin-4 channels*

*BAFFR: BAFF (B-cell activating factor) receptor = TNFRSF13C (TNF receptor superfamily member 13C)*

*BCR/TCR: B/T-cell receptor*

*BRB: blood-retinal barrier*

*CD40: cluster of differentiation 40*

*CNV: choroidal neovascularization*

*DD: death domains*

*FADD: Fas-associated protein with death domain*

*IL-1R1: IL-1 receptor type 1*

*I $\kappa$ B: inhibitor of NF- $\kappa$ B*

*IKK: I $\kappa$ B kinase*

*JNK: Jun N-terminal kinase*

*KIR channels: K $^{+}$ -inwardly rectifying channels*

*MAPKs: mitogen-activated protein kinases*

*MLKL: mixed lineage kinase domain-like pseudokinase*

*MMPs: matrix metalloproteinases*

*NEMO: NF- $\kappa$ B essential modulator*

*NF- $\kappa$ B: nuclear factor- $\kappa$ B*

*NIK: NF- $\kappa$ B-inducing kinase*

*RANK: receptor activator of NF- $\kappa$ B*

*RIPK1: RIP (receptor-interacting serine/threonine-protein) kinase 1*

*T2bs: TRAF2 binding site*

*TACE: TNF- $\alpha$  converting enzyme = ADAM17 (a disintegrin and metalloprotease 17)*

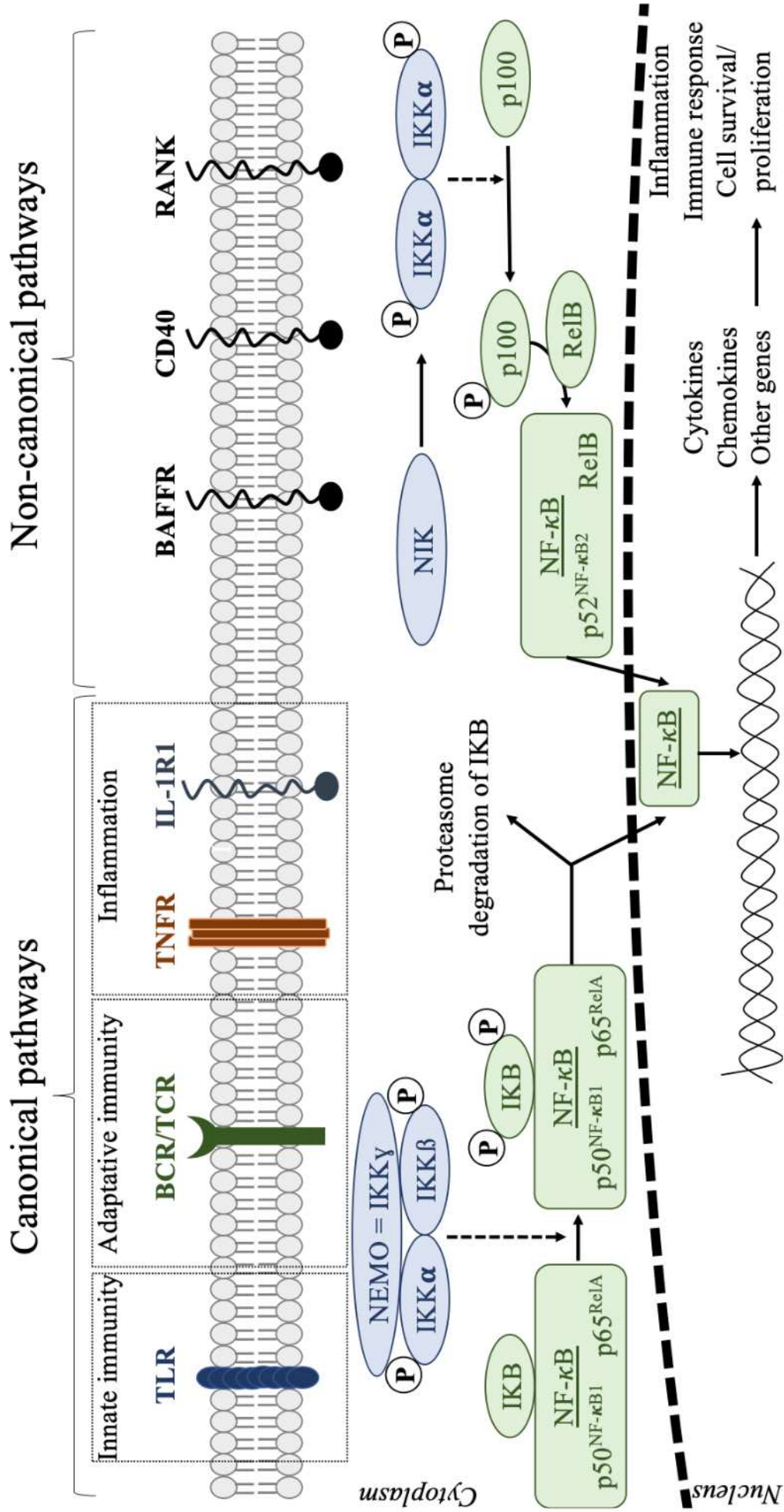
*TLR: toll-like receptor*

*TNFR: TNF receptor*

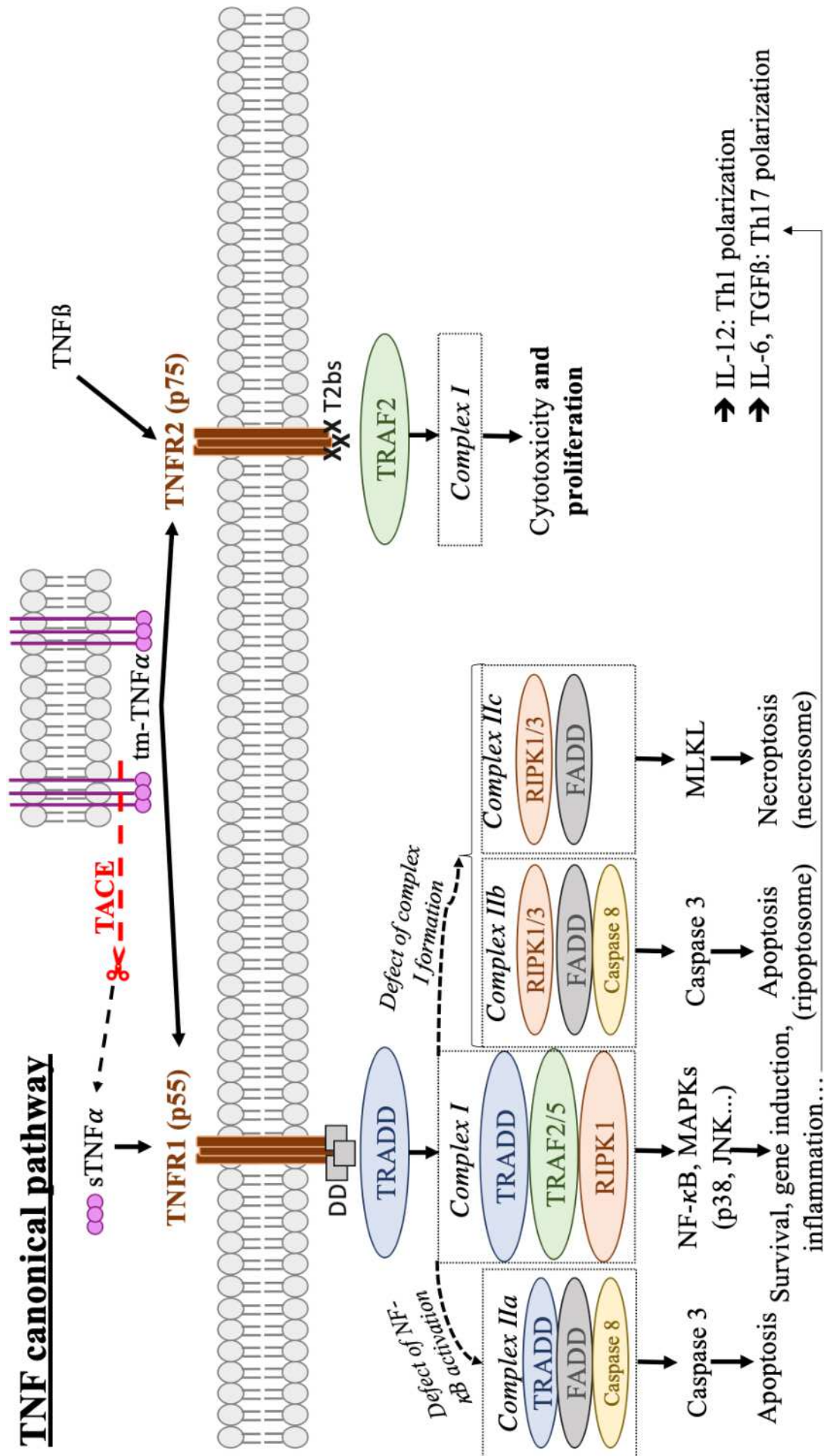
*TRADD: TNFRSF1A associated via death domain*

*TRAF2: TNF receptor-associated factor 2*

# NF-κB pathways

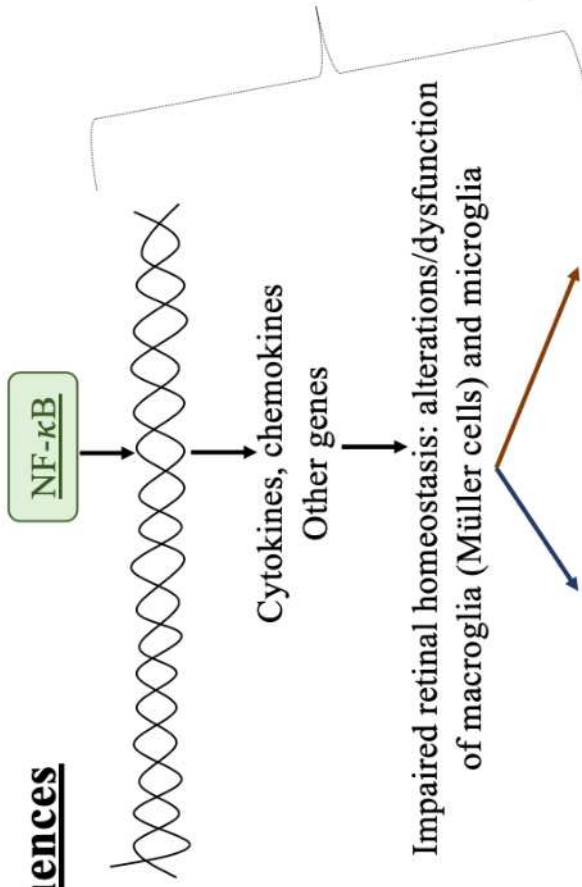


## TNF canonical pathway





## NF-κB ocular consequences



- Co-factors:
- Vitreomacular traction/epiretinal membranes → stress of few Müller cells → secretion of inflammatory cytokines
  - Macular ischemia → increase of extracellular glutamate → alteration of AQP4 and Kir4.1 channels
  - Chronic ME sequelae with Müller cells apoptosis
    - Inflammatory CNV
  - Contiguity with papillary swelling

### CYTOTOXIC ME

- Microglia cells alterations
- Müller cells alterations, especially of KIR channels distribution (which mediate the buffering of extracellular  $K^+$ )
  - o Physiological state: Kir4.1 next to retinal blood vessels with AQP4 channels for blood evacuation of  $K^+$  and  $H_2O$
  - o Pathological state: Kir4.1 uniformly spread or next to external limiting membrane → intracellular and subretinal edema

### VASOGENIC ME

- Pro-inflammatory cytokines secreted by microglia cells and Müller cells: VEGF (VEGF-A especially),  $TNF\alpha$ , IL-1 $\beta$ , prostaglandins... and by other cells → increase in vascular permeability → breakdown of **inner** BRB
- Müller cells secrete more MMPs (MMP-9 especially) → impaired occludin of tight junctions → breakdown of **outer** BRB

## Supplementary material S3.

Personal treatment algorithm proposal based on:

- Quartier-Dit-Maire P, Saadoun D, Belot A, Kaplanski G, Kodjikian L, Kone-Paut I, et al. Protocole National de Diagnostic et de soins sur les Uvéites Chroniques Non Infectieuses de l'enfant et de l'adulte. 2020
- Massa H, Pipis SY, Adewoyin T, Vergados A, Patra S, Panos GD. Macular edema associated with non-infectious uveitis: pathophysiology, etiology, prevalence, impact and management challenges. Clin Ophthalmol. 2019;13:1761-77

### Abbreviations:

ADA: Adalimumab

AZA: Azathioprine

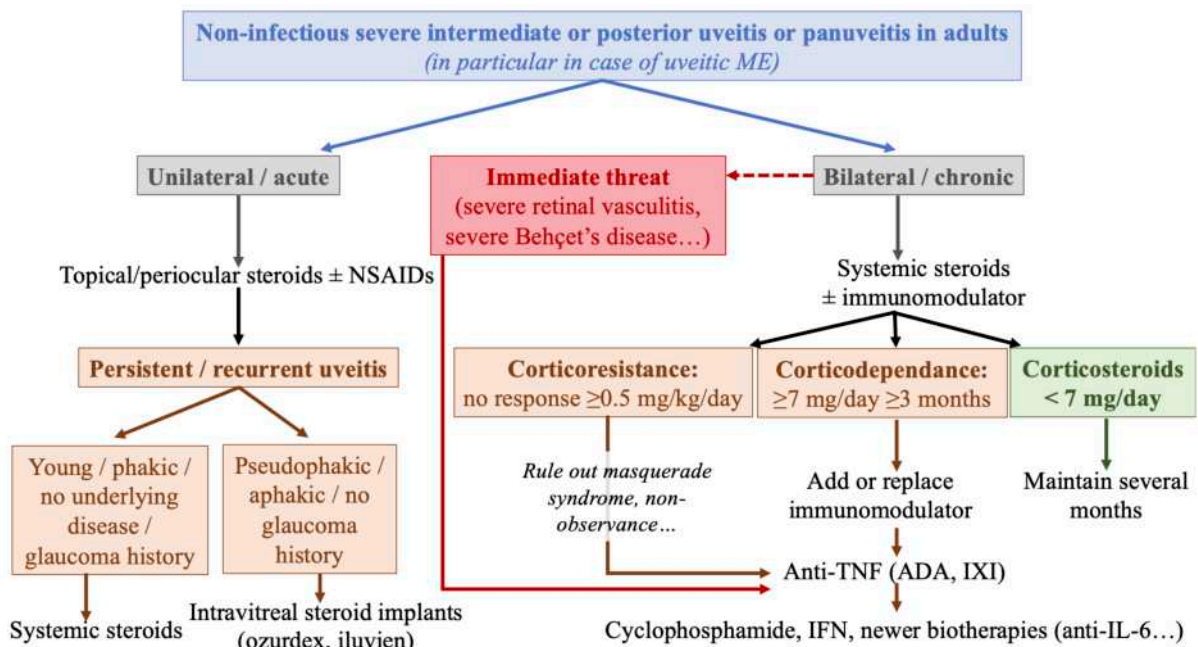
Cys: Cyclosporine A

IFN: Interferon

IXI: Infliximab

MMF: Mycophenolate Mofetil

MTX: Methotrexate



## Supplementary material S4.

Personal work based on several references:

- Thalayasingam N, Isaacs JD. Anti-TNF therapy. Best Pract Res Clin Rheumatol. 2011;25(4):549-567. doi:10.1016/j.berh.2011.10.004
- <https://pharmacomedicale.org/medicaments/par-specialites/item/anti-tnf-alpha>

### Abbreviations:

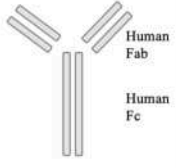
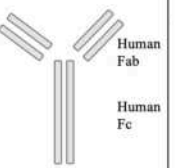
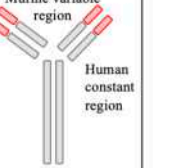
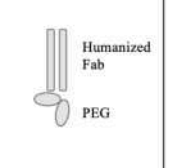
*Fab*: fragment antigen binding

*Fc*: fragment crystallizable region

*LT $\alpha$ 3*: lymphotoxin alpha 3

*mAb*: monoclonal antibody

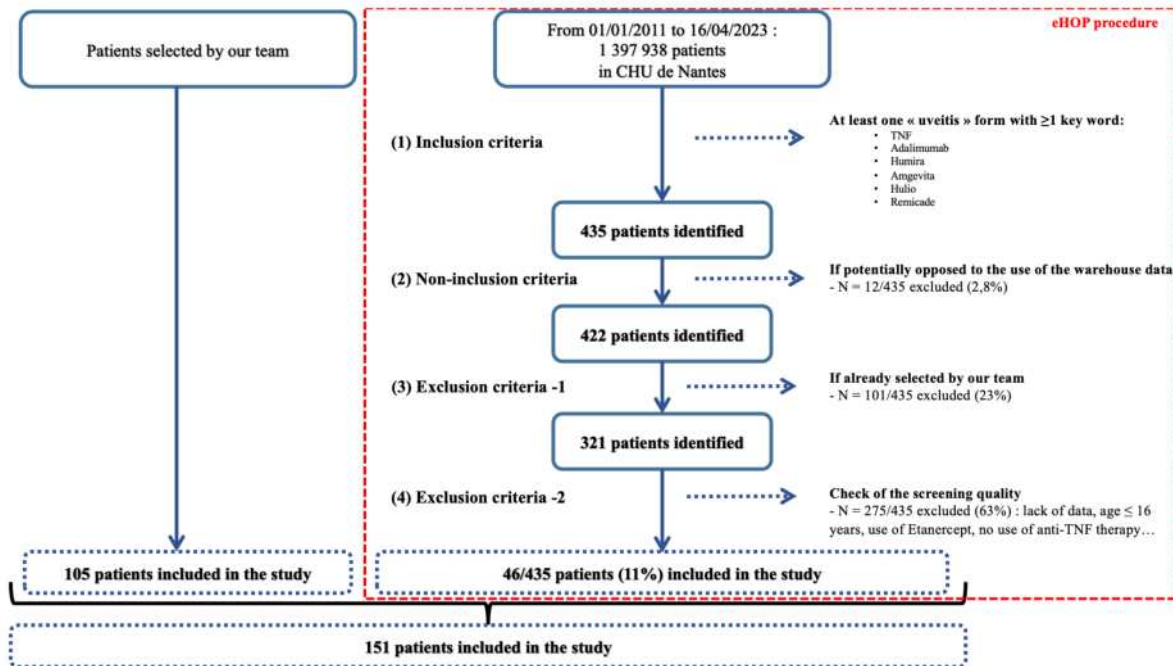
*PEG*: polyethylene glycol

Structure	Monoclonal antibody (mAb) [IgG1]				Fusion protein
	Full-length mAb			Humanized Fab (-zumab) conjugated to PEG	Fusion protein (-cept) of two TNFR2 receptor extracellular domains and the Fc fragment
	Fully human (-mumab)	Chimeric (-ximab)			
					
Name	<b>Adalimumab</b>	<b>Golimumab</b>	<b>Infliximab</b>	<b>Certolizumab</b>	<b>Etanercept</b>
Drugs (non-exhaustive list)	<b>Humira, Amgevita, Hulio, Idacio, Imraldi, Amsparity, Hukyndra, Hyrimoz, Hefia, Kromeya, Libmyris, Solymbic, Yuflyma...</b>	<b>Simponi</b>	<b>Remicade, Remsima, Inflectra, Flixabi, Zessly...</b>	<b>Cimzia</b>	<b>Enbrel, Benepali, Erelzi, Lifmior, Nepexto...</b>
Ligand	TNF	TNF	TNF	TNF	TNF + LT $\alpha$ 3
Molecular weight (kDa)	150	150	150	<b>95</b>	150
Half-life (days)	10 – 20	9 – 15	9 – 12	14	3
Initial dose and treatment interval in adults	40 mg subcutaneous /2 weeks, 1 week after loading dose of 80 mg	Subcutaneous /month	IV /2 months after loading at weeks 0, 2 and 6	Subcutaneous /2 weeks	Subcutaneous /week



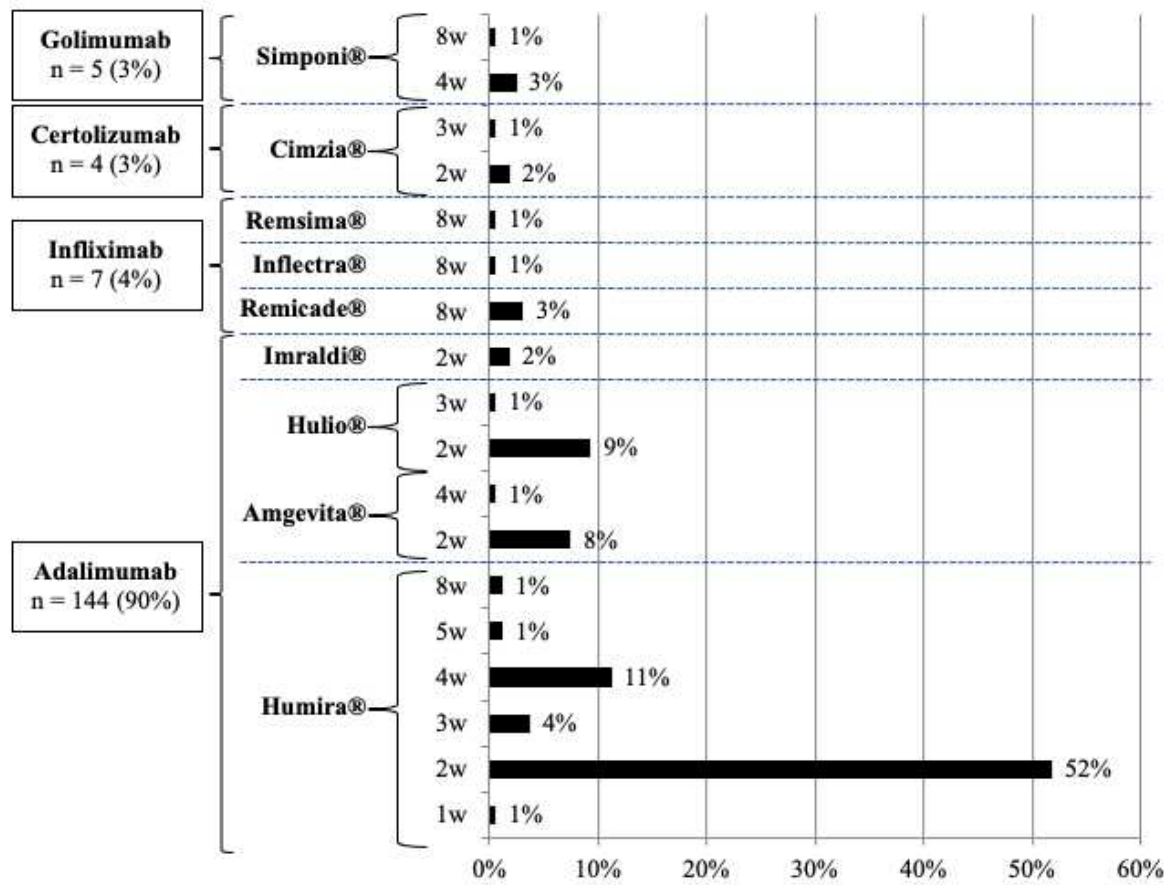
## Supplementary material S5.

Flow chart of the study.



## Supplementary material S6.

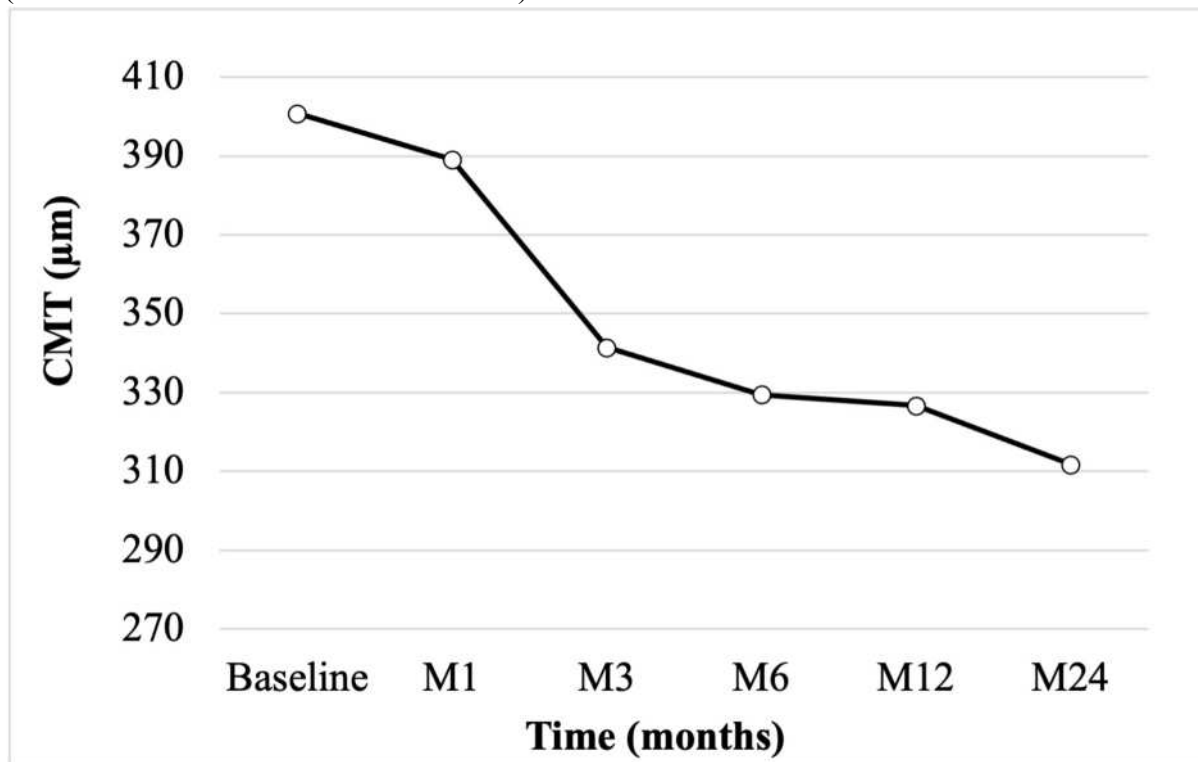
Used anti-TNF therapies and treatment intervals, expressed in weeks (w).



## Supplementary material S7.

Efficacy of anti-TNF therapies in reducing CMT in patients initially treated for macular edema.

**S7A.** Changes in CMT, from baseline to M24, in patients treated initially for macular edema (alone or associated with another reason)



**S7B.**

CMT	CMT, mean $\pm$ SD ( $\mu\text{m}$ )	Mean decrease versus baseline, %	CMT $\leq$ 260 $\mu\text{m}$ , %	CMT $\leq$ 300 $\mu\text{m}$ , %	Available paired data, n (%)	CMT differences versus baseline, mean [95% CI]	p-value
Baseline	401 $\pm$ 121	/	9	24	/	/	/
M1	389 $\pm$ 146	3	10	25	57 (49)	33 [5; 61]	<b>0.024</b>
M3	341 $\pm$ 87	15	11	41	93 (80)	56 [35; 77]	<b>&lt; 0.001</b>
M6	330 $\pm$ 80	18	11	48	91 (78)	75 [53; 97]	<b>&lt; 0.001</b>
M12	327 $\pm$ 94	18	12	48	100 (86)	74 [52; 97]	<b>&lt; 0.001</b>
M24	312 $\pm$ 76	22	21	57	81 (70)	89 [59; 119]	<b>&lt; 0.001</b>

*Changes in CMT in patients treated initially for macular edema (alone or associated with another reason).*

*All 116 eyes were included when data were available, and all available paired data were analyzed for calculating the differences compared to baseline.*

## Supplementary material S8.

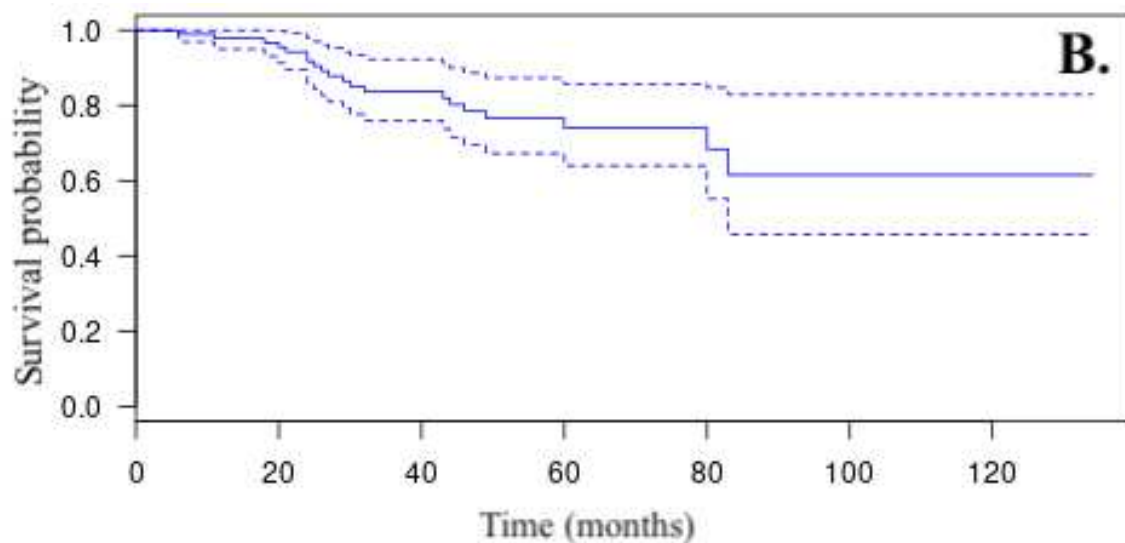
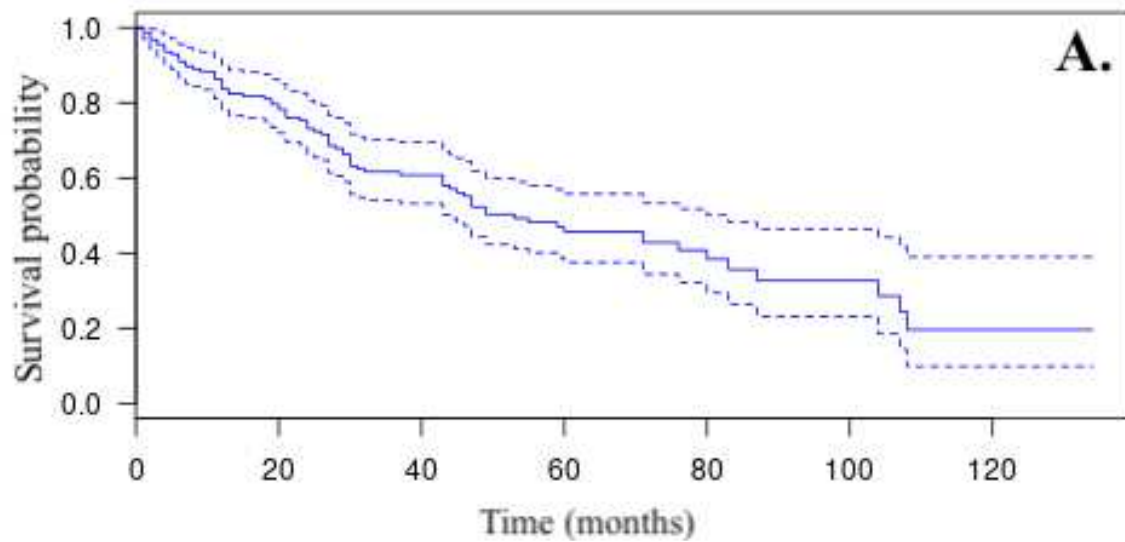
Kaplan-Meier curves of survival probability without discontinuation of the treatment:

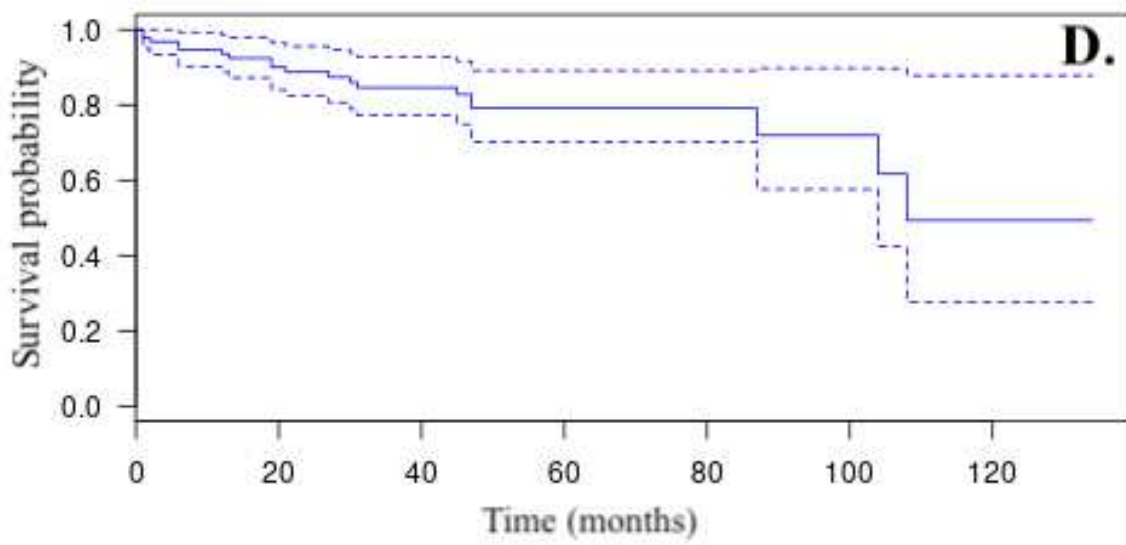
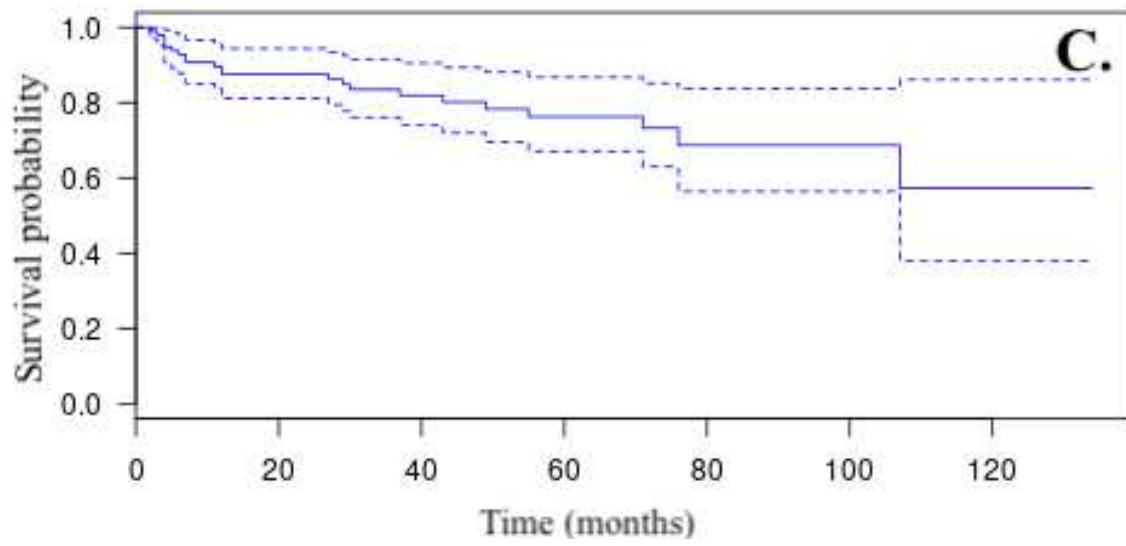
A. **Overall** (every patient except these lost to follow-up before any discontinuation)

B. **For remission** (every patient who did not discontinue the treatment, or did for remission)

C. **For lack/loss of ocular efficacy** (every patient who did not discontinue the treatment, or did for a lack/loss of ocular efficacy)

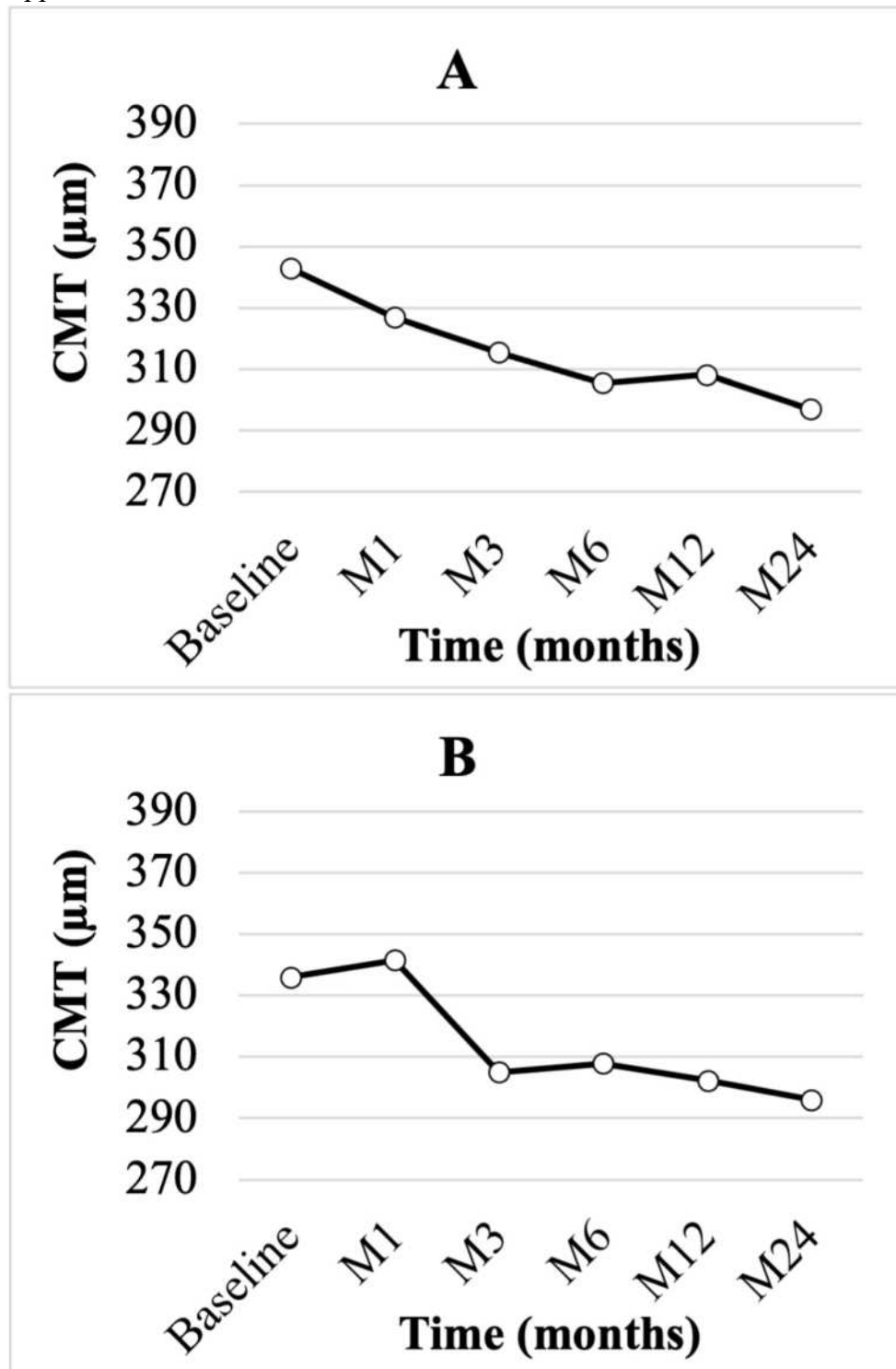
D. **For safety reasons** (every patient who did not discontinue the treatment, or did because of any AE)





### Supplementary material S9.

Changes in CMT, from baseline to M24, according to the intake (A) or not (B) of additional immunosuppressant or immunomodulator.



## INDEX

### **Tables index**

*Table 1.* Baseline demographics and clinical characteristics of the patients.

*Table 2.* Characteristics of used anti-TNF therapies.

*Table 3.* Characteristics of used adjuvant therapies.

*Table 4.* Changes in logarithmic VA (LogMAR) from baseline to M24.

*Table 5.* Changes in CMT from baseline to M24.

*Table 6.* Changes in LFM from baseline to M24.

*Table 7.* Changes in vasculitis rate from baseline to M24.

*Table 8.* Changes in MD for patients with Birdshot chorioretinopathy from baseline to M24.

*Table 9.* Anti-TNF discontinuation.

*Table 10.* Anti-TNF discontinuation over time.

*Table 11.* AEs occurrence.

### **Figures index**

*Figure 1.* Changes in mean logarithmic VA from baseline to M24.

*Figure 2.* Changes in mean CMT from baseline to M24.

*Figure 3.* Changes in mean LFM from baseline to M24.

*Figure 4.* Changes in vasculitis rate from baseline to M24.

*Figure 5.* Changes in MD for patients with Birdshot chorioretinopathy from baseline to M24.

*Figure 6.* Kaplan-Meier curve of overall survival probability without discontinuing the treatment.

**NOM : QUINTART**

**PRENOM : Pierre-Antoine**

**Titre de Thèse : Anti-TNF $\alpha$  dans les uvéites chroniques non infectieuses : une étude observationnelle rétrospective à propos de 151 patients**

---

**RESUME :**

**Objectif :** le but de cette étude était d'évaluer l'efficacité et la sécurité des anti-TNF $\alpha$  chez les patients atteints d'uvéite non infectieuse chronique ou récurrente.

**Méthodes :** les patients ont été inclus rétrospectivement dans cette étude monocentrique au CHU de Nantes. Les données ont été recueillies, si disponibles, avant l'initiation du traitement, un mois après (M1), à M3, M6, M12 et M24. Nous avons recueilli des informations démographiques (sexe, âge), sur le traitement (type, indication), son efficacité (acuité visuelle à distance (AV), laser flare meter (LFM), épaisseur maculaire centrale (EMC), présence d'une vascularite rétinienne, champ visuel en cas de chorioretinopathie de Birdshot), et sa sécurité.

**Résultats :** 151 patients ont été inclus (160 traitements). La plupart étaient des femmes (60 %) avec un âge moyen de  $46 \pm 17$  ans. L'anti-TNF généralement utilisé était l'adalimumab (90 %) pour une inflammation (56 %), en deuxième ligne d'épargne corticoïde (54 %). Cela a permis une épargne significative avec une dose de corticoïde inférieure à 7 mg par jour chez 80% des patients. Moins d'un tiers des patients présentait une uvéite idiopathique et les diagnostics les plus fréquents étaient la sarcoïdose, la chorioretinopathie de Birdshot, la maladie de Behçet ou des pathologies rhumatologiques. La diminution de l'EMC et du LFM était statistiquement significative à chaque rendez-vous. L'AV s'est améliorée de façon significative à partir de M6. Nous avons également observé une amélioration du taux de vascularite, et de la déviation moyenne (Mean Defect (MD)) au champ visuel en cas de chorioretinopathie de Birdshot. Nous n'avons pas objectivé de nouveaux problèmes de sécurité, les principaux effets indésirables rapportés étant des douleurs ou des effets cutanés, avec peu d'infections graves ; mais la prudence reste de mise concernant le risque de réactivation de tuberculose ou de démyélinisation. 70% des patients qui ont arrêté le traitement pour rémission n'ont pas récidivé.

**Discussion :** cette étude souligne l'efficacité et la sécurité des anti-TNF en vie réelle.

---

**MOTS-CLES :** anti-TNF $\alpha$ , uvéite chronique non infectieuse, vie réelle.