

Behçet's syndrome and ocular involvement: changes over time

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ABSTRACT

Ocular involvement in Behçet's syndrome still represents a challenge for both rheumatologists and ophthalmologists; over the past 20 years the availability of new diagnostic tools and the concomitant introduction of biologic drugs have led to a significant improvement in the management of these patients. However, the lack of uniform definitions and the diversity of the outcome measures still represent an obstacle for the prompt and correct management of ocular manifestations.

The aim of the present review is to summarise the current evidences related to correct diagnosis and proper management of patients with Behçet's syndrome and ocular involvement.

Introduction

Behçet's syndrome (BS) is an autoimmune rare disease, classified as vasculitis. It is a syndrome with multisystemic involvement characterised by recurrent oral aphthous ulcers, genital ulcers, skin lesions, and both anterior and posterior uveitis (1). Individual patients develop all of the symptoms with various combinations and that is why the treatment should be customised depending on the clinical manifestations.

Ocular manifestations have a prevalence that varies between 50–70%, can lead to sight-threatening complications and are characterised by recurrent attacks of ocular inflammations involving the eye from the anterior to the posterior segment (2). The risk of blindness, mainly due to macular involvement or retinal vasculitis, increases progressively reaching 25% at 10 years and remains constant thereafter (3). For this reason, a proper treatment in order to suppress the intraocular inflammation, to preserve visual acuity and to prevent the recurrences must be started immediately (2-5).

The aim of this work is to outline,

through an analysis of the literature, what have changed in ocular Behçet's syndrome in the last 20 years in terms of clinical patterns, diagnosis and prognosis.

Clinical patterns and diagnosis: new technologies available for an early diagnosis

Although in recent years much diagnostic and therapeutic progress has been made, clinical manifestations and presentation of BS slightly changed. Ocular inflammation in BS can be the first manifestation in 20% of cases (6-7) and can involve all the uveal tract; for this reason, uveitis can be anterior (11%), posterior (28.8%) or panuveitis (60.2%) (3). Vitritis without anterior or posterior segment involvement and in the absence of angiographic leakage were classified as intermediate uveitis (3) which is more common in early onset BS than in late onset (8). The eye may be involved 2 to 3 years after the beginning of the extraocular signs (7). Initially, the involvement is unilateral with a remitting-relapsing course, becoming then bilateral. Usually, the posterior segment of the eye is the main site of inflammation. Uveitis seem negatively associated with genital ulcers ($p<0.0001$), gastrointestinal involvement ($p=0.008$), pseudofolliculitis and central nervous system signs ($p=0.031$), vascular involvement ($p=0.002$) and erythema nodosum ($p=0.013$) (9). Late onset BS, despite a relatively mild course, could be associated with a higher rate of blindness (10.5%) as recently reported by Saadouli *et al.* (10).

Anterior uveitis is rarely isolated, frequently accompanied by posterior involvement and always non-granulomatous. At the slit-lamp examination, the ophthalmologist can observe Tyndall effect and sometimes a sterile hypopyon that can also be present due to the inflow and the sedimentation of

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neutrophils into the aqueous humour; it reflects the severity of the uveitis (11) (Fig. 1). Currently, Avci *et al.* observed the value of some haematological parameters: platelet-to-lymphocyte ratio, mean platelet volume and neutrophil-to-lymphocyte ratio; that significantly differed among healthy controls and patients with BS and anterior uveitis. Specifically, the latter displayed a stronger relation with anterior uveitis in BS patients (AUC 0.725; $p < 0.001$) (12). Patients with anterior inflammation usually complain about blurred vision, photophobia, tearing, pain and redness. Frequent relapses may be associated with the appearance of some inflammatory complications, such as anterior and/or posterior synechiae, a convex profile of the iris and angle-closure glaucoma (Fig. 1). Generally, glaucoma in BS patients is a late feature associated with relapses or topic and systemic cortico-therapy (13). Cataracts, keratic precipitates, episcleritis, scleritis, conjunctival ulcers, and corneal immune ring opacities are part of the list of other less common anterior segment findings in these patients (14-16). Posterior uveitis may include the presence of hyalitis, retinal vasculitis, mainly venous and often occlusive, macular oedema and/or foci of necrotising retinitis (7, 17) (Fig. 2). Vitreous floaters, vitreous cells, condensations and snowballs (vitreous aggregations of inflammatory cells) can be easily identified if the posterior segment is involved. Vitreous Tyndall is the most important indicator of the inflammatory activity. Fundus examination in case of posterior involvement may be extremely difficult. Moreover, uveitis can be complicated by the appearance of cystoid macular oedema and branch retinal veins occlusions. Cystoid macular oedema can be solved with appropriate treatment or evolve in a chronic macular damage with structural changes that can permanently affect the visual acuity such as macular holes (18). Behçet-related panuveitis is more frequent in men than in women (95.4% men 89.9% women) (4), repeated episodes of posterior inflammation can lead to the end-stage of the disease: vessels become sclerotic and white after multiple epi-

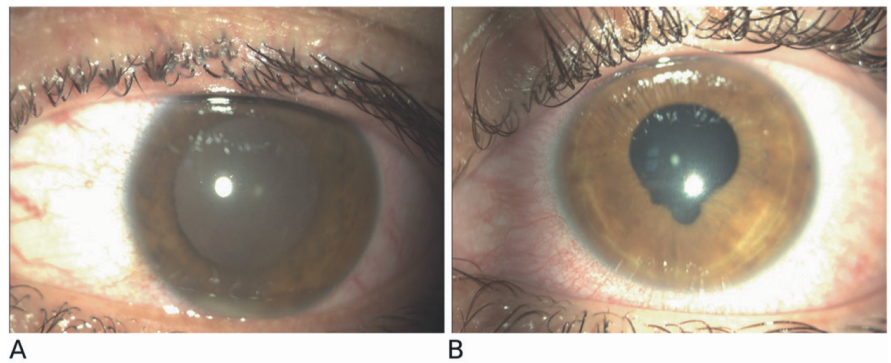


Fig. 1. Anterior uveitis. Sterile hypopyon in the anterior chamber (A), posterior synechiae with iris profile distortion (B).

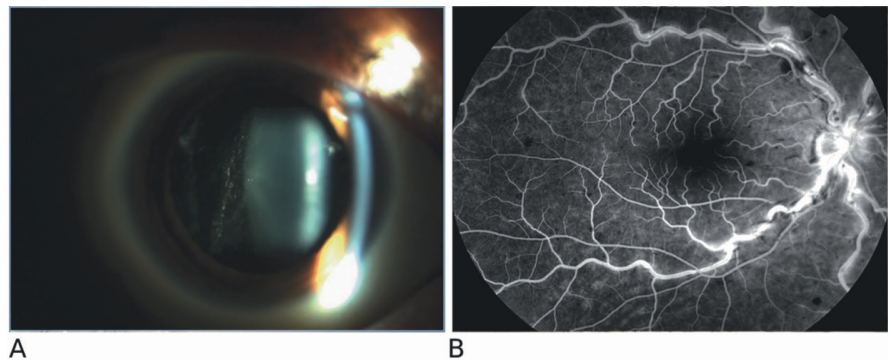


Fig. 2. Posterior uveitis. Vitreous tyndall (A), fluorescein angiography of a patient with retinal vasculitis (B).

sodes of retinal vasculitis and occlusion causing optic atrophy (5, 17-19).

During the past twenty years the development of new technologies has been very useful and demonstrated the crucial role of early diagnosis and follow-up of patients. Nevertheless, the gold standard for diagnosis is still based on clinical examination, and is related with the ocular features observed at the slit-lamp and described following the recommendation of the Standardisation of Uveitis Nomenclature (SUN) working group in 2005 (20). Despite the effort of the SUN international workshop, clinical examination remains subjective and poorly sensitive. Tugal-Tutkun *et al.* recently proposed an algorithm for the diagnosis of Behçet's uveitis in adult patients, using classification and regression trees analysis. The algorithm was based only on characteristic clinical findings and the most relevant items for diagnosis of BS were: the presence of superficial retinal infiltrate or its sequel, retinal nerve fibers layer thickness defect, signs of occlusive retinal vasculitis, and diffuse

retinal capillary leakage on fluorescein angiography in absence of granulomatous anterior uveitis or choroiditis in patients with vitritis (21). In addition, nowadays, there are several diagnostic tools that can help clinicians in the diagnosis and monitoring of both clinical manifestations and complications. These instruments are objective, less operator-dependent and they provide quantitative measurements; therefore, they should be considered as complementary rather than exclusive tools.

Laser flare and cell photometry was introduced in 1988 for the quantification of protein and cells in the anterior chamber (22). It is a fast and non-invasive technique that measures the amount of light scattered from particles while a laser beam is projected into the anterior chamber (23, 24). It provides an objective and accurate assessment of the degree of inflammation on both cellular and protein components. Laser cell photometry allows to monitor the evolution of the inflammation under treatment and to detect first signs of recurrences. Tugal-Tutkun *et al.* in 2010

demonstrated a relationship of laser flare measurement with complications in uveitis and visual loss suggesting that this method could be included in the follow-up routine of patients with uveitis for early detection of recurrences (24). Scheimpflug camera is a device that allow imaging from the anterior corneal surface to the posterior lens surface; it is characterised by a greater depth of focus than traditional camera, as the plane of its lens is tilted and intersects the film plane and the focal plane. It is used to study corneal parameters. Scheimpflug camera does not represent a routine examination for the diagnosis of Behçet uveitis; nevertheless, it may provide explanation for anterior segment findings in patients with BS and ocular involvement during inactive period. In BS corneal thickness and corneal volume were significantly thinner than in healthy controls, while astigmatism and anterior and posterior corneal elevation were higher than in control groups. Elevated cytokine and inflammatory mediators in the cornea and aqueous humour together with higher systemic cytokines may justify these changes (25). Fluorescein and indocyanine green angiography represent the gold standard to detect the haemodynamic changes of retinal and choroidal circulation and a correlation between angiographic findings and final visual prognosis in BS patients has been described. Wall staining, vascular macular and disk leakage as well as macular ischaemia and neovascularisation represent the most common features in BS patients (26-27). BS patients with vasculitis may benefit also of ultra-wide-field retinal imaging to better quantify the extent of the inflammation, to program the treatment and to follow-up the patients (28-29). Optical coherence tomography (OCT) is a non-invasive instrument that allows a detailed examination of the posterior pole of the eye using different scanning modes, linear or circular, also adjusting scan size in length or diameter. OCT allows early detection of any morphological changes in the retina, with the possibility to measure and quantify retinal thickness change (30-33). Central macular thickness and macular volume were signifi-

cantly thicker in macular uveitis with posterior involvement (30-31). Central macular thickness demonstrated also a positive correlation with flare values (32). Subsequently, OCT technology has moved from the methodical Time Domain to the Spectral Domain and recently to the Swept Source technology. Spectral Domain and Swept Source OCTs display greater spatial and temporal resolution, are faster, and offer the possibilities to display ocular tissues such as choroid and sclera in an incredibly narrow time frame. Degiriranci *et al.* demonstrated that macular oedema was the most common complication during the active phases of the inflammation (39.7%); while epiretinal membrane was more frequent during remission (50.6%) together with ellipsoid zone damage (18.2%), external limiting membrane damage (13%), retinal nerve fibre layer damage (14.3%) and macular atrophy (9.1%). Moreover, during remission macular thickness was lower than in active period (30).

Recently, OCT has also been proposed for anterior segment assessment in order to identify inflammatory signs. Anterior segment-OCT could be used for a comprehensive assessment of the anterior chamber, providing objective measurements of inflammatory cells and aqueous flare. Cells appear in the anterior chamber as hyper-reflective dots (34).

The last generation of OCTs are represented by the angio-OCT (OCT-A), that using different algorithms, are able to visualise retinal vascular structures without contrast media and with high resolution (35). This method opens up new scenarios for studying and understanding retinal and choroidal pathologies and pathophysiology. Angio-OCT could be, therefore, helpful and a complementary diagnostic tool in Behçet patients with retinal vasculitis and macular involvement (36). Somkijrungrui *et al.* monitored macular ischaemia by Angio-OCT, and observed that the deep capillary plexus was more affected in BS than the superficial capillary plexus. The authors concluded that macular ischaemia and deep capillary plexus loss were strictly connected with visual prognosis (37). These ob-

servations were confirmed also by the findings of others research groups that observed a larger foveal avascular zone during the remission period in the Behçet's uveitis group and accordingly, a lower foveal and parafoveal vessels densities (38, 39). Interestingly, vessel density appeared inversely related to the number of ocular relapses and cannot be restored during time (40). Even in patients with BS but without ocular involvement OCT-A may detect alterations in superficial and deep vascular density and subfoveal choroidal thickness before the emergence of evident clinical findings (41-42). In conclusion, multimodal imaging modalities through the combination of colour fundus photography, fluorescein and indocyanine green angiography, OCT and OCT-A could accomplish a complete evaluation of retinal and choroidal involvement in Behçet uveitis (42, 43).

Treatment change: are biologic agents the new paradigm?

Currently, the milestones of the treatment are corticosteroids topic and/or systemic and cytostatic drugs, combined or not. These drugs are commonly used depending on the severity and the morbidity of the disease (45-48). The therapeutic choice will depend on signs and symptoms, uni- or bilateral ocular involvement, degree of inflammation, risk of side effects and the patient's therapeutic compliance (45). In 2008, the evidence-based European League Against Rheumatism (EULAR) recommended that any patient with BS and inflammatory eye disease affecting the posterior segment should be on a treatment regimen that includes azathioprine (AZA) and systemic corticosteroids (46). Moreover, if the patient had severe eye disease, defined as 2 lines of drop in visual acuity on a 20/20 scale and/or retinal disease (retinal vasculitis or macular involvement), it was recommended that either cyclosporine A (CyA) or infliximab (IFX) should be used in combination with azathioprine and corticosteroids; alternatively, interferon-alpha (IFN-alpha) with or without corticosteroids could be used to suppress the ocular inflammation and to prevent irreversible damage

that mostly occurs early in the course of the disease (46). Ten years later, in 2018 the EULAR recommendations stated the individualisation of the treatment as overall principle to prevent irreversible organ damage. In addition, if the posterior segment of the eye was the main site of inflammation, treatment regimen should involve drugs such as: azathioprine (level of evidence: IB and a strength of recommendation: A), cyclosporine-A (level of evidence: IB and a strength of recommendation: A), interferon-alpha (level of evidence: IIA and strength of recommendation: B) or monoclonal anti-tumour necrosis factor-alpha (anti-TNF-alpha) antibodies (level of evidence: IIA and strength of recommendation: B). Systemic glucocorticoids should be used only in acute inflammations and in combination with azathioprine or other systemic immunosuppressive agents, especially if the posterior segment was involved (level of evidence: IIA; strength of recommendation: B). High-dose glucocorticoids, infliximab or interferon-alpha should be used in patients presenting an initial or recurrent episode of acute sight-threatening uveitis. Intravitreal glucocorticoid could represent a possible choice in patients with unilateral exacerbation as an adjunct to systemic treatment. (Level of evidence: IIA; strength of recommendation: B) (48). Refractory patients should be treated with IFN-alpha or monoclonal anti-TNF antibodies in order to improve visual acuity and for a sustained response as well as high remission rates. Infections, patients' tolerability and physician's experience could influence the treatment choice. Another alternative is to switch between interferon-alpha and monoclonal antibodies in case of adverse events or in case of primary or secondary unresponsiveness (49-50). Over the past twenty years, immunosuppressive agents have dominated the field of treatment of BS with variable degrees of success. EULAR recommendations suggested the use of azathioprine, combined or not with steroids, at the recommended dose of 2 to 2.5 mg/kg/day in case of ocular manifestations. AZA is a good steroid-sparer treatment and seems to be effective in

preventing relapses and visual acuity in case of posterior ocular involvement without retinal vasculitis (46, 48-51).

The efficacy of CyA when associated with corticosteroids and other immunosuppressive agents such as AZA, is variable according to the manifestations of BS. The EULAR 2008 recommendations proposed the use of CyA, in a dose of 2-5 mg/kg/day, as an effective therapy in arresting the inflammatory activity in the eye and resulting in a rapid improvement in visual acuity (46, 48, 52-54). This improvement remained stable after 24 months follow-up compared to a monthly administration of 1 gram of intravenous bolus of cyclophosphamide in a single masked trial described by Ozyazgan *et al.* (55). The advent of biologic agents with immunomodulatory actions has increased the interest of both physicians and pharmaceutical companies in conducting clinical trials in BS; the EULAR update in 2018 stressed on the importance of the experience with biological agents in patients with BS and ocular involvement (48, 56-60).

Several prospective and open label studies have shown the efficacy of IFN-alpha in the care of patients with BS and severe ocular manifestations (61-66). Main advantages of the use of IFN-alpha is the ability to induce a persistent and prolonged remission of the disease even after the treatment has been suspended. Actually, there is no consensus about the ideal dose and duration of the treatment for Behçet's uveitis (63-64).

In recent years, also anti-TNF-alpha drugs have been evaluated for systemic vasculitis, with contradicting results. Anti-TNF-alpha drugs are a valid alternative for those patients with severe uveitis who are refractory to other treatments or when the disease is poorly controlled by standard immunosuppressive drugs (67).

Strong recommendations indicate adalimumab (ADA) or infliximab (IFX) as the first- or second-line corticosteroid-sparing agents in ocular BS with the latter showing a response rate of approximately 90% (68-71). Intravenous infusion of IFX, used at the dose of 5 mg/kg every 6-8 weeks, was effective

in reducing ocular relapses and maintaining visual acuity. Tabbara *et al.* demonstrated the long-term superiority of IFX compared to conventional therapy. In this study, it was observed that after 36 months a greater visual acuity and a reduced number of relapses from 5 to 17 months. Moreover, ocular complications such as optic atrophy and phthisis occurred only in a small percentage of patients (67). Even if with limited experience, also biosimilar infliximab has been used in patients refractory to conventional immunosuppressive agents and obtained similar safety and efficacy outcomes (72).

In 2007, there was a first case series describing the effect of ADA in sight-threatening uveitis (73). Subcutaneous injections of ADA at the dose of 40 mg every two weeks seemed to be effective in reducing the inflammatory flare, improving the visual acuity and reducing the recurrences of retinal vasculitis after 11, 21 and 24 months of follow-up. In 2017 Fabiani *et al.* retrospectively analysed the efficacy and safety of ADA as a standard stand-alone treatment, or in combination with disease-modifying anti-rheumatic drugs and in patients firstly treated with ADA compared to patients previously administered with other biologics. The primary endpoint was the reduction of ocular inflammatory flares, while secondary endpoints were the improvement of best corrected visual acuity and the improvement of optical coherence tomography and angiography findings. All endpoints were successful and significantly achieved (74).

In a comparative study of IFX *versus* ADA for Behçet's uveitis refractory to conventional non-biologic treatment, ADA appeared to be associated with better outcomes than IFX after 1 year of follow-up. The ocular parameters in which ADA had significantly better outcomes compared to IFX were: improvement in anterior chamber inflammation (92.31% *vs.* 78.18% for IFX), improvement in vitritis (93.33% *vs.* 78.95% for IFX), and improvement in best-corrected visual acuity (mean \pm SD 0.81 \pm 0.26 *vs.* 0.67 \pm 0.34 for IFX) (75). However, corticosteroid sparing effect of IFX was superior than the one of ADA (76).

Recently, cytokine dysregulation in aqueous humour sample of patients with BS has been documented; main cytokines involved were interleukin-1 (IL-1), IL-2, IL-6, IL-8, IL-13, TNF- α , interferon- γ , granulocyte colony-stimulating factor. Interestingly, cytokine's concentration positively was correlated with immune-cells concentration (77). IL-1 blocking agents such as anakinra (ANA), canakinumab (CAN) and gevokizumab have also been used with satisfactory results in terms of visual acuity maintenance in refractory patients (78-82). Emmi *et al.* in a multicentre retrospective study evaluated the efficacy and safety profile of ANA (100 mg/die) and CAN (150 mg/6-8 weeks) in 30 patients affected by BS of whom 16 had ocular involvement. Resolution of symptoms without serious adverse events was observed over 24 months of follow-up. (78). IL-1 blocking agents demonstrated also to be good steroid-sparing agents and their use induced a remarkable disease control not only in refractory cases, but also as a first-line biologic agent (78). Tocilizumab (TCZ) is a recombinant humanised monoclonal antibody that acts as an anti-interleukin 6 (IL-6) receptor antagonist and inhibits both membrane-bound and soluble IL-6 receptors. TCZ used at the dose of 8 mg/kg intravenously/monthly, showed a good response in a small group of patients with ocular Behçet involvement and refractory to anti-TNF- α and/or IFN- α drugs (83). Current medical literature demonstrated that some patients could benefit from TCZ, but this subgroup is yet to be determined (58, 84).

Medical literature also describes the use of other non-TNF-targeted biologics drugs, sekukinumab, daclizumab and ustekinumab (85-87). Their use has been reported in some isolated case reports. Sekukinumab and daclizumab vs. placebo did not show any significant differences either for visual acuity improvement or as a sparing agent (69-70). Ustekinumab instead, has been used in a single case of BS with anterior uveitis. The patient remained symptom-free and relapse-free for at least 36 months (62).

Unfortunately, the diversity and vari-

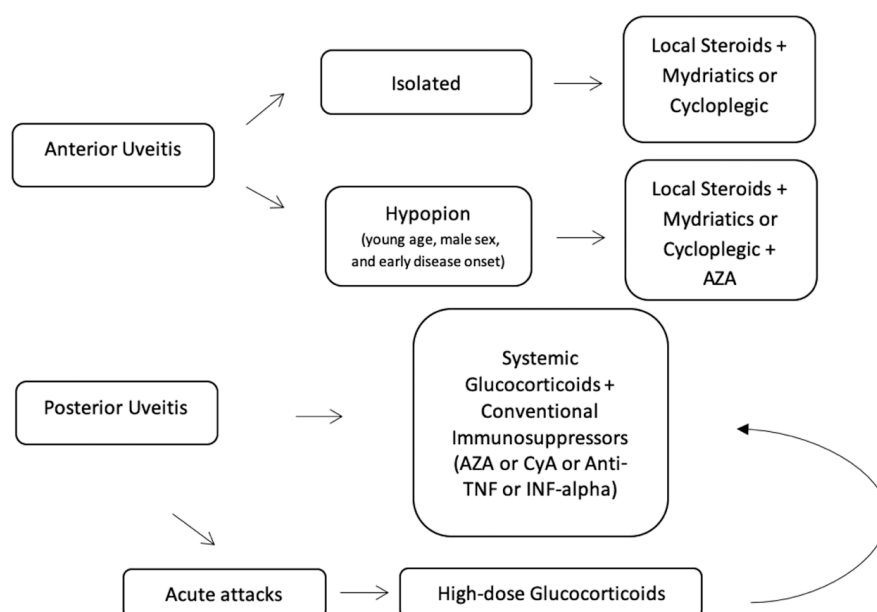


Fig. 3. Uveitis treatment.

AZA: azathioprine; CyA: cyclosporine A; Anti-TNF: anti-tumour-necrosis factor; INF- α : interferon α .

ability of the outcome measures in different BS clinical trials make it difficult to compare their results, combine findings into meta-analyses or guide physicians on management strategies; factors such as clinician's experience, adverse events, patients' preferences, comorbidities, and reimbursement policies play a role in treatment decision-making (60, 88, 89). Better designed comparative studies on Behçet's uveitis will improve our treatment strategies in the near future.

Prognosis

The improvement of the diagnostic techniques, an early diagnosis and a prompt immunosuppressive therapy have shown a trend for better visual prognosis over the past 20 years.

Nevertheless, visual prognosis in patients suffering from BS still represents a challenge. Most patients come to the attention of the ophthalmologist already with a serious posterior eye involvement and with a delay of about 9 months (3, 10, 90-92). It has been widely demonstrated that the visual prognosis is favourably affected by a proper treatment (3, 92, 93), and any delay in starting the therapy increases inflammatory tissue damage and the risk of involvement of the other eye. In a review, Khirallah *et al.* summarised the epidemiology of

systemic and ocular clinical features of BS with particular focus on risk factors, clinical manifestations, complications, and prognosis of Behçet's uveitis (90). Patients treated after 1990 had a reduced risk of blindness in comparison with patients treated in the 1980s (91, 92). The risk of blindness at 1, 5 and 7 years has reduced respectively from 9, 26 and 31% in the 1980s to 5, 16 and 21% in the 1990s (92, 93). Tugal-Tuktun *et al.* confirmed that the visual prognosis improved after the 2000s (3). This improvement was concomitant with the introduction of the immunosuppressive drugs and the use of the interferon- α in patients affected by BS (94, 95). Moreover, Cingu *et al.* reported fewer severe ocular complications in patients who presented in the early 2000s in comparison to patients who presented in the 1990s (96).

Conclusions

In conclusion, from our analysis it appears that ocular clinical patterns slightly changed in the last decades.

There are still too many patients who come to the specialist's attention with a serious eye involvement and with a significant reduction in visual acuity.

Treatment should be customised depending on clinical patterns, degree of inflammation, frequency of recur-

rences and presence of complications. A flow chart summarised the published evidences for the treatment of Behçet-related uveitis (Fig. 3). Moreover, treatment choice would be based on patient characteristics, such as risk of infections, including tuberculosis with monoclonal anti-TNF antibodies, and tolerability of interferon-alpha, physician's experience with these agents, and reimbursement policies of each country. As already highlighted, outcome measures of different clinical trials are different and demonstrate great variability. For this reason, the effort of the academic community should be directed to standardise diagnosis and management of Behçet's uveitis. New technologies could display a fundamental role in this direction.

Biologic drugs such as IFN-alpha and anti-TNF agents, are currently recommended as a first-line biotherapy especially in patients non-responsive to the classic immunosuppressive treatment and with frequent relapses.

In refractory and multi-resistant cases, there are initial evidences of safety and efficacy of other non-TNF-targeted biologics drugs such as sekukinumab, daclizumab and ustekinumab.

Actually, the management of uveitis in these patients requires close collaboration between an expert ophthalmologist and rheumatologist. It would be ideal to standardise the care of Behçet patients with ocular involvement. Obviously, this goal requires a great effort, considering the innumerable geographical differences in disease expression from the Mediterranean basin to the North of Europe or America, also considering the different possibility of access to treatments and the availability of biological drugs in different regions.

Take home messages

- Behçet's syndrome still represents a challenge for clinicians with a relevant risk of blindness.
- New diagnostic tools may help clinicians in diagnosing and monitoring clinical manifestations and complications.
- Customised treatments could be regarded as the new target both for rheumatologists and ophthalmologists.

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