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Advancing Prognosis in Behçet's Uveitis: The Role of Biologic Therapies

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Abstract | **Review Article**

Behçet's disease (BD) is a chronic, multi-system inflammatory disease with potentially devastating ocular involvement. Uveitis remains one of the leading causes of blindness in BD patients. The usual remedies, mainly corticosteroids and immunosuppressants, do not effectively work long term and/or stop relapses. New medicines have changed treatment. New therapies for Behçet's uveitis may just address the cause of the disease process. This paper analyses the continuous evolution of biologics and their contribution towards improving prognosis; specifically it examines tumour necrosis factor (TNF) inhibitors, interleukin (IL) antagonists, and other monoclonal antibodies. Drugs like infliximab and adalimumab have been quite helpful in controlling inflammation, preventing relapses, and saving sight. These agents target immune pathways to ameliorate the systemic and ocular manifestations of BD, and they have a better safety profile than traditional agents. Rising proof points out that IL-17 and IL-1 inhibitors may also work, opening the choice of therapy for resistant cases. Even though they have made progress, there is still a lot of work to do and overcome optimization biologics challenges related to the patient, cost, and adverse effects. This review highlights the value of personalized treatments, offering key recommendations for the use of biologics in their overall management approach depending on the severity. Also, real-world studies and head-to-head trials will help refine therapeutic algorithms in the future directions. Doctors may use biologic therapies to greatly enhance the quality of life and the visual outcome in Behçet's uveitis. It is an important step toward precision medicine in BD.

Keywords: Behçet's uveitis, Biologic therapies, Tumor necrosis factor inhibitors, Interleukin antagonists, Precision medicine.

1. INTRODUCTION TO BEHÇET'S UVEITIS

Behçet's uveitis (BU) is a significant ocular manifestation of Behçet's disease (BD) [1]. Ocular involvement is autoimmune and inflammation within the uveal tract of the eye is usually bilateral and recurrent, occurring with extraocular signs such as mouth ulcers or genital ulcers, which are diagnostic criteria for BD [2]. Eye involvement is sight-threatening and is usually one of the most common causes of irreversible blindness in BD [3]. The uveal tract of the eye consists of structures, such as the iris, ciliary body, and choroid, which nourishes the other eye tissues and is linked by the blood-ocular barrier [4]. The iris is the anterior uveal structure, consisting of an anterior layer and a posterior layer [5]. The anterior layer is the visible iris, which presents the color of the eye [1]. The underlying stroma consists of the melanocytes and stromal fibers and is usually normal in Behçet's uveitis [6]. The posterior layer of the iris is a pigmented epithelium which consists of melanocytes and acts as the barrier between the posterior and anterior chambers of the eye, allowing the pupil to regulate light entrance into the eye [7]. The ciliary body also consists of the pigmented epithelium on the posterior side and the ciliary epithelium on the anterior side [8]. The ciliary epithelium produces the aqueous humor which fills the anterior chamber and vitreous humor which fills the posterior chamber [9-11].

Epidemiologically, BU has a different occurrence depending on the ethnic group and geographic distribution [12]. The condition is more prevalent in the Turkey-Japan region, as Behçet's disease implies a severe reduction in the quality of life, as it affects young citizens during the most productive years [13]. The prognosis of BD is favorable in terms of survival probability, but the accumulation of damage has been raising considerations about disability rates [14]. It

is crucial that the patients are referred to health services in Developed Countries as soon as the symptoms are noticed [15]. Almost all patients with BD in developed countries start with mucocutaneous lesions, while they initially appear as ocular symptoms in developing countries [16]. The number of people diagnosed with BD is rising worldwide due to its autoimmune nature [17]. Sample classification methods and the binary and multilabel compatible gadget flow can be used to classify and diagnose BD symptoms, which can contribute to further research on BD [18]. Nevertheless, despite the recent advances in effective treatments, including biologics, ocular prognosis remains inadequate in large patient series, where 30% of patients are further disabled due to ocular involvement [19]. Introduction to new therapeutic targets for BU in the current landscape, such as clinical and experimental data on the janus kinase (JAK) pathway inhibition, the Th17/Treg balance, LCK gene, and several cytokines, contribute to the progression of understanding the pathogenesis of Behçet's uveitis [20-24]. Understanding the pathogenesis of ocular BD will improve the understanding of disease progression in BU patients, as well as the development of new therapeutic targets to prevent ocular symptoms in all BD patients [25-27]. Necessity to build a precious gadget to evaluate the chance of severe ocular involvement in BU and the need for cataract surgery opening the methodology to follow [28].

1.1. Definition and Epidemiology

Behçet's disease was initially described as an entity with recurrent oral ulcers, uveitis, and genital ulcerations in 1937 [21]. However, as the understanding of the disease improved, the spectrum of the disease widened, and new clinical findings were added [22]. Behçet's disease is a systemic, recurrent, chronic, inflammatory, multisystemic vasculitis affecting veins more than arteries [29]. It is characterized by relapsing and remitting courses [30]. Behçet's uveitis arises as the most common ocular involvement in ~70% of the patients [30]. Ocular involvement is the hallmark of morbidity in BD [31]. Results are blindness in rather young patients (median age 25 years) in a previous series [27].

There are well-known geographic distribution and ethnic predisposition to BD. For this reason, prevalence, and clinical spectrum of the disease are quite variable in different geographic parts of the world [32]. The term 'Behçet family' was introduced into the literature because of the striking 'genetic susceptibility' in some families, and the frequency of HLA-B51 was reported as 43-89% in the patients in different series [2]. The use of such an expression must be because of the real incidence of the disease, but the definition gained a designative attribute in the society [33]. Clinically quite different diseases have been evaluated with Behçet's disease. Mulder proposed a higher incidence of some diseases in Eastern Turk patients in the Netherlands compared with white Dutch people [34]. A similar increase in the prevalence, i.e., 12.2:1 in Japan, is reported in a previous series [34]. Modernity in developing countries brings lifestyle changes. Some traditional behavioral and environmental factors may play a role in the onset of BD that can be interpreted as the acquisitional absorption of genetic susceptibility [35]. On the other hand, environmental factors have a role due to strain or virulence changes [36]. Because of all these reasons, imitation is expected but always disputed [36]. Understanding of the geographic and ethnic distribution of the BD is important for the individualized approach in the practice. Moreover, in this way, clinical disciplines and generally practitioners can arrange themselves to the disease in early stage [37]. An early diagnosis approach will also eliminate iatrogenic morbidity [37]. The cultural and geographic variations are effective on the disease onset and course, and disease will appear incubationally [38]. Whereas, clinical studies began with ocular complaints in Japanese and Turkish patients, the clinical onset is arthritis and life-threatening symptoms in Japan [38]. As is seen, the understanding of the BD may differ in different cultural and populations [39]. So, treatment approaches will also modify patients related to the population [39] There are significant differences in the incidence of each clinico-epidemiological picture of the disease in different parts of the world [40]. Behçet's uveal involvement reported as 67-90% in Behçet's disease by using the old diagnostic criteria, is found as 16-50% in new diagnostic approaches in different series [40]. On the other hand, as a subpopulation clinical manifestations, mucocutaneous symptoms were found to be about 82% in BD in a previous series [40]. The awareness of geographic and ethnic sensitivity of each clinical entity is expected to develop various approaches to the disease [39]. So, subpopulation studies can be beneficial for early diagnosis in different risk groups [32]. In addition, the predisposition of ethnic background is useful for the mutation screening of the disease [33]. Population approach to BD is expected to be beneficial for the clarification of multifactorial etiology of the BD [35]. Typically, it is expected to prepare a groundwork for the synthetic clinical and epidemiological definition of the disease, and then etiologic agent(s) and other involved factors of the disease will be understood easily even at the population level [36]. After the discovery of those agents, protection, treatment, and management of the disease will take place [39]. On the other hand, it will eliminate the semantic controversies and assumptive statements that appear and grow from ignorance look above the BI threshold of the disease [40].

1.2. Clinical Manifestations and Complications

Behçet's disease was first described in 1937 with a triad of recurrent oral aphthous ulcers, genital ulcers, and relapsing anterior chamber inflammation in the eye [41]. Ocular involvement is observed in 50–70% of patients with Behçet's disease, and it is the most serious and frequent complication that threatens the vision prospect [21]. Patients often describe eye redness,

pain, and vision changes as the initial symptoms in the onset of the disease [30]. Every part of the eye can be affected, and the inflammation can be of varying type and severity [42]. Clinical manifestations are different in each patient, and a patient may not experience all of the manifestations [43]. Overtime, repeated attacks of inflammation lead to the more distressing complications in the back of the eye, such as glaucoma, cataracts, and retinal damage [44]. Due to these attacks, chronic effects begin to become apparent, compromising normal eye function permanently [45]. In the advanced stage, if the condition is not well contained, severe visual impairment or total blindness results [46].

It is important to recognize at an earlier stage of the disease before the complications settle in order to manage the inflammation effectively [47]. Clinical manifestations within the first year of the onset of the uveitis were found to be significantly associated with a worse prognosis in the visual outcomes, and it determined the prognosis in the entire course of the uveitis [48-50]. A comprehensive evaluation of the clinical manifestations is subsequently imperative in developing an optimal individualized treatment plan that can lead to a better prognosis [51-53]. However, unlike many other uveitis, tough management of both the sight-threatening inflammation within the eye and the underlying disorders makes the treatment even more challenging in patients with Behçet's uveitis [54, 55].

2. Current Treatment Landscape

Managing Behçet's uveitis is challenging, given that a definitive cure has yet to be found. Treatment regimens are still under investigation, as response to specific medications varies among patients [25]. The treatment of Behçet's uveitis has relied mainly on conventional method comprising corticosteroids (CS) and immunosuppressive agents (ISAs), such as cyclosporine, azathioprine and cyclophosphamide [56]. AS is characterized by relapses, and chronic inflammation has an increasingly more significant impact on the poor prognosis disease, which leads to sight-threatening complications [57]. In the initial stages of the disease, the patient will manifest an intense inflammatory response, driven by an increased number of acute vascular thrombosis and chronic vasculopathies in both arterial and venous blood flow [58]. Although a few therapeutic agents may have controlled the systemic manifestations, it is difficult to alleviate the exacerbations within the following relapses [58]. CS and ISAs remain a cornerstone therapy, aiming to control the sight-threatening inflammation as quickly as possible [59]. CS are potent and effective drugs that control the inflammation of the ocular involvement, suppressing the expression of cytokines, enzyme formation, eicosanoids, and bioactive lipids, and control the proliferation of macrophages, T and B-lymphocytes, vascular permeability, etc [60]. However, long-term use can be unfavorable in terms of various local and systemic side effects [61]. ISAs are a group of drugs that act as antineoplastic agents [60]. Their mechanisms of action are not entirely uniform, and they are typically combined with moderate to high doses of corticosteroids [62]. In addition to common side effects (liver function disorders, leukopenia, and so on), others of concern include the exacerbation of inflammatory symptoms due to over-immunosuppression [62]. Furthermore, they are slow to produce an effect, contingent upon maintaining a certain plasma concentration. This threshold value could be toxic, developing acutely: particularly renal fibrosis from cyclosporine therapy, inducing nephrotoxicity [25]. Alongside the potential to damage other organs, it is not a drug suitable for long-term therapy [25]. Despite the high dose of ISAs or refractory to conventional therapies, the effectiveness is different in different patient groups [2]. Early mortality is possible because certain patient groups encounter more aggressive disease [2]. It can be concerning that 1 of every 4 patients may develop disability during the care process [2]. The inflammation of ocular disease that extends to the posterior segment is generally more severe and such patients, rather than anterior segment inflammation is more severe, have shown an abysmal response to ISA therapy [5]. It is of critical importance that these patients be promptly and accurately treated with effective drugs [7]. There is an unquestionable requirement for novel therapeutic approaches in the treatment of uveitis given the limitations of conventional therapies [25]. There are many reasons for this, with the persistence of some patients with sight-threatening complications even when these drugs are fully used, presenting one of the major obstacles [52]. Behçet's uveitis consists of hypopyon, vitreous, and retinal diseases that are less responsive to ISAs, at the forefront of global anti-inflammatory medications [52]. With uveitis, there are many reasons that necessitate the long-term continuous use of anti-inflammatory agents, and corticosteroid-associated complications may arise [53]. Alternatives and co-therapies to ISAs and CS are, therefore, of keen interest [57]. Conversely, the presence of some patients in remission and side effects also arising from the use of anti-TNF agents can make their scheduled use problematic, along with the high costs of treatment [61]. Oral anti-TNF agents were ineffective in multifocal retinal vasculitis [61]. While oral steroids were tapered, 10 mg of oral methotrexate (MTX) was started [62]. Additionally, rifampicin was reduced for her discoloration of the skin [62]. After a definitive diagnosis of Behçet's syndrome, biologic agents were initiated. When uveitis progresses to a severe situation or fails to be inhibited by ISA, treatment by using effective biologic agents is indicated [58]. Phase III clinical trials have confirmed that biologics are beneficial to cases of uveitis that are specific to BD [59]. When ophthalmologists treat Behçet's disease with eye involvement, any refusal to provide treatment using systemic biological agents can result in legal consequences [60]. Management typically hinges on the treatment resorted in the past, the doctor's skills, the patient's history, and evidence-based recommendations,

even though insufficient consensus exists for the diagnosis, treatment methods, or response criteria [61]. Early diagnosis and a comprehensive response are required because the irreversible morbidity pressure from the onset to vision cessation of more than 9% is extremely high [62].

2.1. Conventional Therapies

Behçet's uveitis (BU) is a devastating condition with regard to the visual prognosis [63]. Evidently, time to clinical mitigation or achieving remission is crucial for the prognosis, and early introduction of systemic adjunct therapy should be recommended [2]. In past decades, a variety of treatment modalities have been proposed [3]. Initially, conventional therapies such as corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and immunosuppressive drugs have been widely used and proved effective in controlling the acute inflammation of BU [64]. However, corticosteroids exhibit their efficacy through nonspecific anti-inflammatory action, and the delayed onset of action can result in irreversible vision loss [64]. Long-term and high-dose administration of corticosteroids may lead to serious side effects, while adverse effects often arise before the drugs exert their therapeutic efficacy [63]. Therefore, a new direction aimed at preserving the efficacy while minimizing systemic toxicity has been pursued [63]. This has led to the use of a combination of corticosteroids with well-established non-glucocorticoid components including cytotoxic anti-metabolites, such as methotrexate, cyclophosphamide, and consequently azathioprine [63]. Although traditional immunosuppressive therapies combined with systemic corticosteroids have long served as standard treatment regimens, many clinical investigations have shown that they are ineffective in controlling ocular inflammation [64]. Consequently, the emphasis has shifted toward the investigation of adjunctive therapeutic strategies to enhance the efficacy of corticosteroids [65]. Nonetheless, conventional treatment regimens are far from satisfactory, and a more rational and effective therapeutic decision becomes necessary to improve prognosis and quality of life, particularly for patients with chronic BS since all these long-term complications inevitably occur with BU [66, 67].

2.2. Challenges and Limitations

Despite the widespread use of conventional therapies, including colchicine, immunomodulators, and corticosteroids, response is often suboptimal, and the side effects are intolerable [68]. Response to treatment is highly variable depending on genetic, environmental, and clinical factors, and early diagnosis and detection of uveitis might reduce ocular complications [68]. In addition to genetic factors, climate, living habits, and the genetic background of common infections of the organs not only trigger the onset but also influence the progress [69]. It is noted that country-specific guidelines should exist and be followed [69]. Although guidelines exist, not all physicians follow them, and the major disabilities occur because of incorrect treatments or delays in the proper ones [70]. Furthermore, since actual observations of Behçet's related uveitis are very rare in some national territories; therefore, the experience with the drugs in such cases is insufficient [70]. In general, treatment options are country dependent, and even though information is exchanged globally on a high level today, sometimes it leads to the incorrect use of drugs [71]. There are several critical barriers to the effective management of Behçet's uveitis with conventional drugs, such as the accessibility of effective selective drugs for disease, the high cost of these medications [72]. There is a difficulty in justifying the high cost of ANS therapy over other immunosuppressive medications because the ANS treatment may be significantly more expensive than patients treated with colchicine and minor immunosuppressive [73]. These problems should be particularly considered in the evaluation of ANS for approval in the context of Behçet's uveitis [73]. Compliance with medical therapy is also another problem; taken drugs on a chronic basis is a significant drawback for patients [74]. It is suggested that patients must have a flexible lifestyle in order to remember to regularly take their drugs; otherwise this may result in lower efficacy [75]. Consequently, this reduced compliance may result in resistance of the disease [75]. Chances of this threat increase with time because of the predicted long duration of BD [74]. The consequence is chronic disability, which has socioeconomic implications, particularly in developing countries [76]. Currently used dressings are either inherently toxic or when used in high doses administered over extended time periods, exposing the BD patient to significant toxicity for the remainder of his or her life [76].

3. Biologic Therapies in Behçet's Uveitis

In the past decade, stratified efficacy and tailored therapy have become the key words in treating immune-mediated diseases, such as rheumatoid arthritis and ankylosing spondylitis [24]. Immunosuppressive agents such as cyclosporine, corticosteroids, and azathioprine have been the mainstay treatment of Behçet's uveitis for the past 7 decades [29]. However, with the progress of science and new understanding of immune responses, targeted therapies focusing on various cytokines involved in inflammation cascades have opened a new horizon in treating immune-mediated diseases [20]. Many types of biologic agents are now being introduced for the treatment of Behçet's uveitis, meaning that the treatment strategy in this disease will not end with a maximally tolerated dose or the highest safe level of immunosuppressive agents in controlling inflammation [77]. This means current treatments such as corticosteroids and azathioprine have to be changed to tackle involvement of the eye or the central nervous system [78, 79].

Biologic therapies are different from classical treatments as they focus on specific targets, pathways, and cells of immune cascades and are tailored to control

the inflammatory process [80-82]. The hope lies in the expectation that long-term complications arising from immune control agents may be avoided [83-85]. The overall goals of any adjunctive treatment are to improve the efficacy of controlling inflammation and thus improve the prognosis of uveitis and to be able to safely taper corticosteroid and other control agents [86-88]. Improved efficacy will lead to resolution of intraocular inflammation at an earlier stage, which may in turn minimize complications of uveitis and reduce severe vision loss as a consequence of repeated exacerbations [89].

3.1. Mechanisms of Action

In the last decades, basic science and chemists have developed new molecules to specifically target the various components of the immune system [90]. Trying to prevent inflammatory processes at Th1, Th17, B-line and innate immunity basic levels in Behçet's uveitis is the main reason for assessing biologics in Behçet. Many drugs have been made since 2000 [91]. The targeted cells could be CD20, CCR4, TGFb, IL-6, or IL-17 monoclonal antibodies [91]. And targeting cytokines or genetic blocking could be with receptor blocker or monoclonal antibody [92]. Each of these mentioned drugs will have a different mechanism of action on the subcellular and cellular level [93]. New biotechnologic drugs are currently available that target individual mediators of the inflammatory cascade [94]. Biologics are a form of therapy derived from living substances and are specifically designed to interfere with chronic inflammatory diseases at a very basic level [95]. New biologics are molecules designed to identify and block particularly well characterized biochemical pathways [95]. Beyond the monoclonal antibody family, newer options, such as cytokine inhibitors, have been developed [96]. Conventional immunosuppressive therapy generally inhibits or modulates a broad range of immune cells and soluble immune response mediators which increase the risk of cytopenia, recurrent infections and opportunistic infections [97]. They are also less effective in achieving better control of inflammation than biologic strategies that single out specific cell types or factors in an immune-mediated disease [96]. Consequently, the recently observed increased number of studies aimed at extending the knowledge of their precise effect at a cellular level is not surprising [95]. A better understanding of the interplay between biologics, cells, and cytokines and the combination of these can contribute to the planning of personalized instead of empirical therapy [96]. Treatment could therefore be tailored to the individual patient and be based on the precise pathogenetic interpretation provided by detailed clinical and laboratory investigations [97].

3.2. Efficacy and Safety Profiles

Behçet's disease is a systemic immune-mediated disorder characterized by recurrent episodes of oral and genital ulcers, uveitis, and other manifestations [29]. Uveitis is a serious complication and occurs in at least 50% of Behçet patients, with severe vision loss envisioned in up to 70% of uveitis eyes within 5 years [23]. The irremediable inflammation elsewhere in the eye can cause serious complications and irreversible vision loss, making it difficult to treat Behçet posterior uveitis [98]. However, biologic agents have recently brought new expectations to the treatment of Behçet's uveitis [20].

Behçet's disease is a systemic medium-sized vasculitis that is difficult to treat and varied to some extent according to the affected organ [99]. In that respect, treatment of the vascular occlusions and also uveitis associated with Behçet's disease is still controversial [24]. After many therapeutic attempts, biologics, and immunosuppressive agents gradually demonstrated their effectiveness on BD, especially on BD uveitis [100]. Drugs of at least 6 main classes are employed on patients with Behçet's uveitis [101]. Evidence has shown that biologic agents are appropriate to be started [102].

Though Behçet's uveitis is serious and intractable, recent clinical trial data have reported that biologic therapy has a success rate in reducing ocular inflammation and maintaining visual acuity, although some studies shall cope with their limitations [60]. This paper reviewed the previous studies on biologics in Behçet uveitis, both clinical trials and real-world ones, from which one can compare the rate of success of recent biologic agents with conventional therapy on BD uveitis [103]. The outcomes indicate a high success rate of the biologic arm both in terms of reducing the inflammation in the eye and in terms of preserving visual acuity [104]. The studies also underlined the rapidity of such treatment in achieving a status of relative success in preserving the vision. Moreover, one paper demonstrated the tolerability obstacle of systemic therapy in BD and the favorable safety profile of certain biologics in this population was also discussed [105]. Despite the promising outcomes presented, this review unveiled some lines of thoughts about the biologic therapy in BD that deserves to be re-contemplated for an adequate patient selection and management [106]. These include the relatively high ineffectiveness rate of biologics, higher than azathioprine and cyclosporine and very high, as requires at least one new agent [107, 108].

4. Clinical Trials and Real-World Evidence

For several years, the treatment efficacy of various biologic therapies is being evaluated by many Behçet's uveitis cohorts [109]. Since there is a limited number of head-to-head studies comparing biologic agents, evaluating the effectiveness of biologic therapies in different patient populations will be mentioned [110-113]. Further, as well randomised clinical trials, real-world evidence has a crucial role in broadening the understanding of the outcome of treatment in practical settings and provides insightful data on patient populations that are not included in clinical trials [114-

116]. Thereby, in the light of recent studies, it is aimed to provide a wider perspective on the effectiveness of biologic treatments in Behçet's uveitis, while still stressing the need for future studies investigating the less assessed biologics [117, 118].

In a post-hoc analysis of the Behçet's cohort, mostly white Behçet's uveitis patients with markedly lower DDMS of BD are included compared to another cohort (comprising a similar number of patients of Middle Eastern ethnicity) [119]. After one year of biologic therapy, 73.4% of BD patients from the cohort were in remission whilst only 35.7% of patients from the other eye cohort were in remission [120]. Conversely, the eye cohort patients had much more improved visual acuity tips compared to the BD patients [121]. The disease course and prognosis of BD patients and Behçet's uveitis patients can be markedly different between westernized and Middle Eastern populations [122]. Thus, results of RCTs and observational studies performed in a single population may not be applicable to all Behçet's uveitis patients [123]. There are still unmet needs for strong evidence that can guide choosing the best treatment for refractory Behçet's uveitis patients, which is more difficult than common uveitis types [124]. That is why it is important to assess the effectiveness of different therapeutic options through the analysis of registries and long-term follow-up data of many BD centers installed at different countries and aimed at the same disease [125]. In the field of BD, a number of studies have evaluated the effectiveness and safety of TNFα inhibitors and other biologics since the introduction of these agents for the treatment of refractory manifestations of the disease [126]. Randomized controlled trials were followed by a plethora of observational reports [126]. While various challenges persistently complicate the conduct and interpretation of clinical studies in Behçet's syndrome, to maximise the level of evidence on treatment effects in this disease [127]. Most of the evidences come from open studies, mostly retrospective and involving few cases [125]. After licensing biologics as a treatment for many uveitides, many studies on their application to uveitis have been published [119]. However, as with other fields of medicine, the effectiveness of biologic therapies in uveitis and Behçet's uveitis may strongly differ among a wide variety of patient populations [122]. Despite an increasing number of reports from real-life experience complementing controlled clinical trials, providing reliable information that can efficiently orient choices for treatment remains a critical unmet need for the scientific community [127].

5. Future Directions and Emerging Therapies

As for future directions and emerging therapies, a better comprehension and advanced treatment principles to further address Behçet's uveitis so evident by chronic relapsing form must be established [128]. New, innovative treatment strategies are needed for this disease in order to enhance present options and to overcome new unmet clinical needs [129]. With personalized medicine, it is necessary to profile genetic features to predict and optimize treatment selection precisely [130]. Thus this exhibits promise as a potentially fruitful and valuable approach [131, 132].

In the horizon, it is possible that novel biologic agents could be beneficial about this entity for the foreseeable future [130]. Moreover, in view of the underlying immune pathogenesis which is multifaceted, the experience with multifaceted biologic therapy in recent transplantations, oncologic producing experiments are recognized [59]. Innovative comprehensive treatments that include combination therapy and interventions targeting to all of these pathways might be considerably beneficial for Behçet's uveitis [27].

It is of paramount importance to initiate a multidisciplinary interaction between clinical and research groups of uveitis, rheumatology and immunology [133]. Many opaque points about these entities, which require an understanding and treatment of methodologies are phenomenal, so might be enlightened by collaborations [134-137]. Furthermore, advances in technological capabilities; In particular, the improvement of feedback between patients and doctors with wearable bio-sensors and portable vital parameter measurement units, telemedicine and tele-monitoring systems, could have a profound impact on these chronically treated patients, whose follow-up years continued [138-141]. By exploiting all these approaches, it is perfectly possible to improve prognosis and quality of life in the Behçet uveitis group [142].

In summation; without a doubt, this will provide better management of Behçet's uveitis over the coming years with these strategies, thus currently, it seems an auspicious instance of significant emerging modes of uveitis treatment considering the background of the systemic therapeutic aspect of this wide disease group.

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