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Treat to target in Behcet's disease: Should we follow the paradigm of other systemic rheumatic diseases?

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ABSTRACT

During the last decades the efficacy of biologic agents, mainly of anti-TNFs, in controlling the activity of serious manifestations of Behcet's Disease (BD) has been established. On the other hand, the clinical heterogeneity of BD has precluded the validation of a widely-accepted composite index for disease assessment and for target disease-state definitions, such as low disease activity and remission, and the testing of their implementation in clinical practice. Therefore, in contrast to other systemic rheumatic diseases, a treat-to-target strategy has not yet been developed in BD. There are several challenges towards this approach, including standardization of outcome measures for assessing the disease activity in each-affected organ and construction of a composite disease activity index. The challenges for the development of a treat-to-target strategy and possible solutions are discussed in this position paper, which stemmed from a round table discussion that took place in the 19th International Conference on BD.

1. Introduction

Behcet's disease (BD) or Behcet's syndrome, also known as Adamantiades-Behcet's disease, is a remitting-relapsing inflammatory condition with multiple clinical manifestations, the severity of which can range from mild symptoms to the life-threatening clinical conditions [1]. It is classified among the primary systemic vasculitic diseases and, its pathogenesis, although remains enigmatic, is considered to lie at the crossroads between autoinflammation and autoimmunity with a considerable genetic contribution, which also plays an important role [2–4]. Almost every existing immunomodulatory/immunosuppressive medication has been used for the treatment of BD during the years with variable success rates [5]. During the last decades, significant progress has been made in the management of BD patients with the introduction of anti-TNF agents [4,6]. However, the heterogeneity and possibly the rarity of the disease have precluded the development of robust instruments for proper monitoring of the disease activity. Partially related to that, the desired therapeutic targets (i.e. remission/low disease

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activity) could not be defined. Physicians have usually tailored the treatment according to the patients' individual needs and prognostic factors with the aim of the prevention of relapses and organ damage while preserving the function and quality of life. Side effects of therapeutic agents should be also considered, especially when these are given for non-major clinical manifestations. Nevertheless, due to the lack of validated specific treatment targets, a standard "treat-to-target (T2T)" approach for BD has not been proposed thus far in clinical practice.

T2T has been successfully implemented in various non-rheumatic diseases, including diabetes mellitus, arterial hypertension and chronic obstructive pulmonary disease [7]. Moreover, over the last years this strategy changed the treatment landscape of certain systemic rheumatic diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), leading to favorable results and helping optimization of the treatment [8,9]. Regarding RA the T2T approach is being followed for >10 years and the favorable outcomes of this strategy have been confirmed in many randomized controlled trials [10]. In brief, the T2T strategy is a multiparametric process which has many steps including: choosing the theraoeutuc target, selecting the methods to achieve the target, choosing the time-points of assessments for target-achievement, as well as applying treatment changes in case the goal is not achieved.

Following a round table discussion that took place in the 19th International Conference on BD in Athens, in July 2022 [11], we herein aim in this position paper to delineate the challenges and facilitators for the development and implementation of a T2T approach in BD.

2. The paradigm of systemic lupus erythematosus

Systemic lupus erythematosus (SLE), like BD, is also a relapsing-remitting disease with clinical and immunological heterogeneity and an unpredictable course [12–14]. Due to the inflammatory disease activity and exposure to medications with potentially deleterious effects (especially, glucocorticoids), irreversible dysfunction or damage of various organs (e.g., osteoporotic fracture, muscle atrophy, lung fibrosis) develops in approximately 40–50% of patients within 5 to 10 years after the disease onset [15]. Also, SLE patients are burdened with reduced health-related quality of life that is comparable to other chronic medical disorders [16].

The realization of the aforementioned unmet clinical needs coupled with the approval of novel therapies in SLE for the first time after 50 years [17], stirred up the discussions for the need to define specific therapeutic goals. To this end, an international panel of experts was assembled during 2012–2014 with the aim to appraise the existing evidence and discuss the T2T concept in SLE. The systematic literature search included a total 12 topics focusing on the association between disease activity/flares, organ damage and outcomes, and the relative benefits and harms of specific treatment strategies in SLE [9]. Following grading of the evidence, eleven recommendations were introduced which emphasized the importance to target for remission or the lowest possible level of disease activity, to prevent exacerbations and organ damage accrual, to reduce (or, withdraw) glucocorticoids during the maintenance phase, and to avoid treating serological activity in the absence of clinical activity [9]. Still, there were a number of unresolved issues in particular, how should remission and low disease activity be defined, whether the focus should be on general SLE or specific organ involvement (e.g., glomerulonephritis), and also, whether duration or serological markers should be incorporated in these definitions [18].

Accordingly, a number of candidate definitions of SLE remission and low activity were put forward. The Asia-Pacific Lupus Collaboration introduced the Lupus Low Disease Activity State (LLDAS) which has been extensively validated in large retrospective and prospective cohort studies [19–21]. During the same time, Italian investigators determined the feasibility and prognostic impact of clinical (i.e., with no consideration of serological markers) lupus remission [22,23]. Following a statistical approach, they concluded that a clinical SLEDAI-2 K (SLE disease activity index-2000) of zero was the most critical component for defining remission [24]. Of note, attainment of either LLDAS or clinical remission for a period of at least two years was associated with significantly reduced risk for flares and damage accrual, thus substantiating the treat-to-target approach in lupus.

Based on these findings, a large international panel recently endorsed the DORIS definition of remission in SLE as: i) clinical SLEDAI = 0; ii) physician global assessment of the disease activity <0.5 (on a 0–3 scale); iii) irrespective of serology; and iv) on stable maintenance treatment with any of antimalarials, prednisone ≤5 mg/day, immunosuppressives or biologics [25]. Importantly, the T2T principle has been also endorsed by the EULAR in the 2019 update of the general SLE and lupus nephritis recommendations [26,27]. Ongoing efforts such as the 'BEST' randomized controlled study [28] will hopefully help to further refine the implementation of T2T in SLE care towards improving disease and patient outcomes.

3. Challenges for T2T in BD

Having SLE as an example of variable disease manifestations and treatment responses, one could easily identify the challenges of T2T strategy in BD (Fig. 1). First, diagnosis of BD is clinical and requires a high level of clinical suspicion and expertise, since biomarkers are lacking except from the pathergy test whose sensitivity is relatively low. Second, the treatment modalities vary depending on the type of clinical manifestations and their severity. Of note, commonly used therapeutic regimens are not without adverse effects (e.g. infections, iatrogenic osteoporosis, glaucoma). Third, a single index that measures the disease activity of BD, which takes into account the variety of clinical and laboratory features with appropriate weighing is lacking.The specific target, how often it needs to be assessed, and how stringently it needs to be enforced may be different for each manifestation. Moreover, there are not widely-accepted definitions for the partial and complete remission; hence several different outcome measures have been used across studies. Currently available global disease activity measures such as BD current activity form (BDCAF) fall short of setting treatment targets according to our current understanding of BD. An example is eye involvement, where activity is inquired by"a red eye, a painful eye blurred, or reduced vision". Our current knowledge indicates that lack of capillary leakage on fluorescein angiogram is needed to rule out active uveitis and should be targeted in patients with Behçet's uveitis.

Finally, a central question remains in BD: what is the target? Is the "holy grail" of drug-free remission achievable? [29] And if so, in which patients?

In the next paragraphs, the above-mentioned challenges are elaborated.

3.1. Disease activity

Disease activity in BD patients reflects all possible clinical manifestations including oro-genital ulcers, skin lesions, musculoskeletal, nervous system, ocular, vascular and gastrointestinal involvements at a specific time point (Table 1). Monitoring disease activity is a fundamental issue of the clinical assessments to be able to elucidate health status and the care priorities of patients. It also provides information for the individual treatment plans that are often complex to coordinate [30–35].

One of the characteristics of BD is its fluctuating activity, which is more obvious in mucocutaneous manifestations [30,36–38]. Oral ulcer activity may run in parallel with musculoskeletal [30] and genital ulcer activity [37], as well as with psycho-social well-being [33], all of them affecting the functionality and quality of life [30]. Moreover, increased mucocutaneous activity, as the activity of oral ulcers, may be associated with new major organ involvement in young female BD patients with systemic involvement [39]. It is worth mentioning that oral ulcers may have role in triggering systemic activation, because oral microorganisms and inflammatory mediators could gain access to systemic circulation

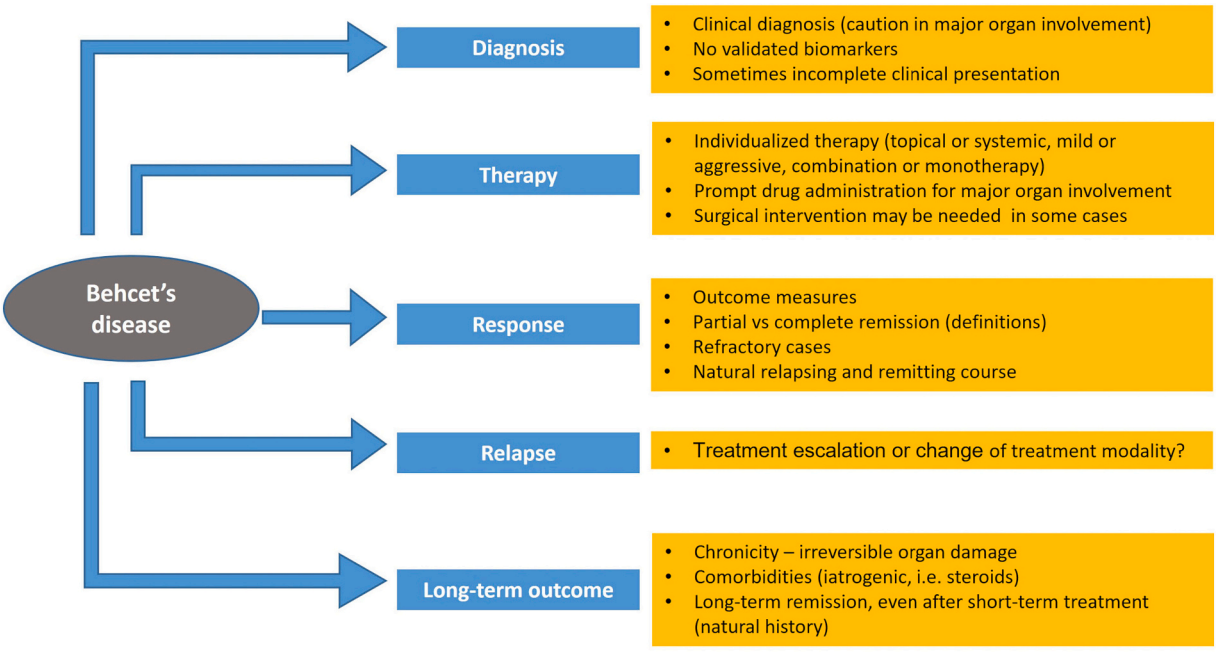

Fig. 1. Main challenges for development of a treat-to-target strategy in Behcet's disease.

Table 1
Outcomes for monitoring disease activity and targets for specific organ/tissue involvement in Behcet's Disease.

Organ/Tissue	Monitoring	Target
Skin, mucosae	Number of lesions QoL	Ensuring quality of life
Joints	Number of affected joints PROs including QoL	Preventing permanent structural damage
Eye	Anterior chamber flare/cells and vitreous haze/cells New fundus lesions Fluorescein angiography Episodes/year BOS24	Actual activity, preserving best residual visual acuity
Vascular	DVT recurrence US/CTA Acute phase reactants	Post-thrombotic syndrome and mortality
Gastrointestinal	Endoscopy Fecal calprotectin	Mucosal barrier integrity
CNS	MRI Cognitive function indices QoL	Preventing permanent cognitive, motor, sensory damage

BOS24: Behçet's disease ocular attack score 24, CNS: central nervous system, CTA: computed tomography arteriography, DVT: deep vein thrombosis, MRI: magnetic resonance imaging, PRO: patient reported outcomes, QoL: quality of life, US: ultrasound.

through the disruption of the mucosal barrier [36,40,41].

Oral aphthous ulcers are often the sole manifestation of the disease, denoting some clinical activity in many BD patients without any other findings [35,37,42–44] and are managed with mild agents such as topical CSs or colchicine, to prevent side-effects. In some of these cases, aphthous ulcer-free state cannot be achievable despite the remission of all serious disease manifestations, and using a terminology like "low or minimal disease activity" may be considered to define the partial response of mucocutaneous manifestations to therapy in clinical practice [35,36]. However, the definitions of "low or minimal disease activity" in BD is not yet clear. Along the same lines, definitions of complete remission, partial remission, relapse, refractory disease [37,45,46] and irreversible functional and anatomical damage attributed to BD [47,48] should also be clarified.

Of note, measurement of disease activity by using a disease-specific global activity index has been challenging in BD owing to its multiple organ involvement [34,49]. Instead, the evaluation of ongoing therapies and activities of isolated organ involvement are usually assessed by organ specific activity indices [33,43,50]. Apart from the clinical findings, patient reported outcomes are used as tools for the assessment of the disease activity with questions relevant to a wide range of disease manifestations, and also some indices, like those measuring functional limitations,for the measurement of the burden of disease and also its effects on the daily life activities [49,51].

However,it is fairly difficult to compare results obtained so far from the different indices and scoring methods;therefore, consensus guidelines with inputs from all stakeholders should be re-defined for each organ system involvement to be able to use in clinical practice as well as in clinical trials.

3.2. *Outcome measures*

Distinction between the disease activity and irreversible functional and anatomical damage can often be difficult. However, the Core Set of Domains for outcome measures developed by the OMERACT BD working group may be a useful guide in determining the organ-specific targets [52], This core set was developed through a multistep process that comprised a systematic review of outcomes and outcome measures that had been used in BD studies, focus group meetings involving different stakeholders including physicians, researchers, patients and members of pharmaceutical industry, semi-structured interviews with patients, and a 3-step Delphi among BD experts and patients [52–54]. In addition to the domains that would be assessed in all patients, separate domains were developed for the specific assessment of each organ or system involvement. Domains that would be assessed in all patients included: overall disease activity, new organ involvement, quality of life, adverse events, and death. Domains for specific organ involvement were: number and pain of lesions for the mucocutaneous involvement, tender and swollen joint count for the musculoskeletal involvement, frequency of attacks, visual acuity, ocular severity and vascular leakage for the ocular involvement, vascular lesion, superficial thrombophlebitis and post-thrombotic syndrome for the vascular involvement, central nervous system lesion, cognitive function and neurologic function for the

nervous system involvement, and clinical gastrointestinal activity and endoscopic activity for the gastrointestinal involvement (Table 1). Efforts are ongoing to determine the best outcome measures and instruments to assess these domains, and for developing new ones if none of the available instruments are optimal for a specific domain.

From a T2T point of view, this core set constitutes a framework for identifying the targets for each type of involvement in BD patients. However, there is still an important amount of work required to determine the ideal specific target, as well as how and how often it should be assessed for each organ involvement.

3.3. Defining the target

Defining the treatment target is a crucial part of developing T2T strategies. Remission or low disease activity states determined using a composite index have been successfully used as treatment targets in diseases that are relatively homogenous in terms of organ involvement, such as rheumatoid arthritis. However, a different approach may be required for BD, which is a complex multisystem disorder where complete remission and lack of relapses is the necessary target for some manifestations, whereas low disease activity may be acceptable for others without an effect on the prognosis of the patients, with the aim of obtaining optimal benefit with minimum risk of treatment-related adverse events. Thus, different targets for different types of organ involvement may be preferred to a single treatment target for all patients with BD. Recurrence of oral aphthous ulcers usually does not cause a damage and does not leave a scar. However, in some of the disease manifestations, new flares may lead to irreversible organ damage, which is well established for the flares of posterior uveitis and for parenchymal neurological or vascular disease [55]. Therefore, the updated 2018 EULAR recommendations for the management of BD state that the goal of treatment is to promptly suppress inflammation in order to prevent irreversible organ damage and reduce recurrences, which subsequently worsens the damage [56]. The concept of T2T relies on identifying targets that are feasible to assess in daily practice and that are associated with long term good outcomes. A small number of studies provide clues on such targets for different organ manifestations of BD. For example, in patients with ocular involvement, fundus fluorescein angiography findings showing ongoing peripheral capillary leakage predicted relapses and a “dry” angiogram was associated with a good long-term visual outcome [57,58]. For venous involvement, lack of good recanalization of venous thrombosis on Doppler ultrasonography was the most important predictor of relapses [59]. Prevention of post-thrombotic syndrome which is present in a considerable percentage of BD patients and is associated also with impaired quality of life in these individuals, could also be a target for venous involvement in the setting of BD [60]. For gastrointestinal involvement, endoscopic mucosal healing is associated with lack of relapses, and a negative fecal calprotectin test was associated with endoscopic remission [61].

Unfortunately, no standard targets to define the therapeutic success in BD exist [52,62]. A meta-analysis on the efficacy of interventions for oral ulcers in BD concluded that because of a heterogeneity of trial designs, choice of intervention, choice and timing of outcome measures, variable level of disease activity and changes in the concurrent medications, it was impossible to carry out a meta-analysis examining the targets for the treatment response in even just oral aphthous ulcers of BD [62].

Since then, focusing on each individual organ-system, studies have shown that indeed heterogeneity in study designs hampers the possibility to compare treatment-targets. A recent analysis of head-to-head studies with biologic drugs in ocular BD included 6 RCT’s and 3 large retrospective studies [63–72]. Many different outcome parameters were employed with most of the studies using visual acuity. There is not much more homogeneity and possibilities to compare these studies other than that each individual study has a positive conclusion on its own. If it comes to finding targets in these studies the primary endpoints and power analyses of the RCT’s can be evaluated (Table 2). Remarkably, only half of these studies mentioned a preset endpoint. Most endpoints and definition of therapeutic success in those studies varied significantly.From these data it can be concluded that each study has used different interpretations of therapeutic success meaning inactive disease. Similar conclusions can be drawn from analyses of other organ specific head-to head studies in BD as well [56,60,73–88] (Table 2).

4. Discussion

In general, T2T strategies are helpful to prevent damage and preserve organ function and optimize patient and disease outcomes, however solid evidence on how to achieve them is not readily available for many

Table 2
Head to head trials in Behcet’s disease.

First author, Date	Primary endpoint	Power
Ocular BD		
Nguyen, 2016	Treatment failure	Difference > 15%
Jaffe, 2016	Time to treatment failure in 6 weeks	Not done
Davatchi, 2010	Overall state Total Adjusted Disease Activity Index	Not done
Buggage, 2007	Number of ocular attacks Amount of immunosuppressives	Not done
Dick, 2013	Reduction of uveitis recurrence Proportion recurrence <24 weeks Reduction of vitreous haze score	Relative reduction of 65% (SHIELD) Difference of recurrence rate 0,30 Difference of 0,8 ISM score
Lightman, 2015	<10 mg prednisolone throughout 10–12 months	Difference between 5% and 60% in the treatment group
Mucocutaneous BD		
Yazici, 1990	Developing terminal events	Not done
Hamuyurdan, 1998	Complete response during 24 weeks	Difference of 35% in response rate
Alspoy, 2002	Observational	Not done
Melikoglou, 2005	Suppression pathergy and MSU	Not done
Hatemi, 2015	Oral ulcers at week 24	Difference of 0,65
Sharquie, 2002	Observational	Not done
Grayson, 2017	Proceed to phase two study	CR oro-genital ulcers during 2 visits 3–6 months
Matsuda, 2003	Global improvement aphthous count and pain	Not done
Takeno, 2022	AUC oral ulcers 12 weeks	Not done
Hatemi, 2019	AUC oral ulcers 12 weeks	Difference of 66
Yurdakul, 2001	Complete response during 24 weeks	Not done
Mat, 2006	Difference mean number genital ulcers	Difference of 30% in response
Vascular BD		
Ahn, 2008	DVT recurrence (CTA or Doppler US)	Retrospective
Desboid, 2012	DVT recurrence (CTA or Doppler US)	Retrospective
Alibaz-Oner, 2015	Mortality DVT recurrence (CTA or Doppler US)	Retrospective
Hatemi, 2018	Meta-analysis: relapse rate, RR 0,17 for IS	Not done
Emmi, 2018	Observational: clinical and imaging	Retrospective
Articular BD		
Yurdakul, 2001	Complete remission arthritis	Not done
Davatchi, 2009	IBDDAM	Not done

BD: Behcet’s disease, ISM: immunosuppressive medication, MSU: monosodium urate, CR: complete remission, AUC: area under the curve, DVT: deep vein thrombosis, CTA: computed tomography angiography, US: ultrasound, RR: relative risk, IBDDAM: Iranian Behcet’s Disease Dynamic Activity Measure.

diseases. Also, there are several barriers that impede the proper application of T2T strategy in everyday clinical practice. These include: physicians' and patients' perceptions about drugs efficacy and safety, socioeconomic aspects like access to healthcare facilities, lack of resources (T2T strategy often demands frequent visits), adherence to medication and others [89,90].

To summarize, the following questions/suggestions should be taken into account when developing a T2T strategy for BD: First, how do we measure disease activity in BD? Is there space for a composite index? Distinction between mild (aphthous ulcers and joint manifestations) and severe flares (posterior uveitis, vascular and/or parenchymal neurologic involvement) as well as distinction between disease activity and disease damage, as in other diseases is also important [91–93]. Second, a consensus is needed even for measuring disease activity in organ-specific manifestations in BD, such as ocular, neurologic, vascular and intestinal involvement. Third, which is the optimal therapeutic target in BD? Disease remission is a reasonable thought, also from a humanistic perspective, but what does that mean in a multisystemic disease? One thought would be to give the most attention to some organ systems for which irreversible organ damage might occur with relapses. Potential targets and long term goals can be organ specific and were recently proposed, but need to be validated in prospective studies [94]. Besides, quality of life and patient experiences are other important targets. For example recurrent ulcers do not leave permanent damage. However, they cause serious distress for the patients and affect significantly their quality of life. Towards this direction, patients' participation is the design of clinical trials and in the decision of the desired outcomes is fundamental [95]. Of note, patients' and physicians' aspects about optimal treatment outcomes and/or the rank by which these should be achieved, is not always the same [96]. Finally, can we achieve drug-free remission [29] and can the early administration of biologic agents modify the disease course?

The above-mentioned questions/considerations should take into account that there has been a tremendous progress in the field of BD therapeutics, especially with the introduction of biologic targeted therapies in 2001 [97], which have changed the natural history of the disease, especially regarding the preservation of the best residual visual acuity [6,97,98]. Of note, newer biologic and targeted synthetic DMARDs are also tested with promising results in various aspects of BD [4,80,81,99].

Apparently, the development of such recommendations would have to be tested and implemented in clinical practice. This, would have to take into account certain aspects that are related to a. *access to care* (financial/social differences among countries, access to rheumatologists), b. *clinicians* (awareness of the T2T concept), c. *patients* (adherence to medication, perception of the disease), d. *systematic issues* (time-consuming documentation of disease activity indices) [90].

Taking the main strands together, we believe that there is a need for the formulation of recommendations about a T2T strategy in BD, by experts in the field, including rheumatologists, ophthalmologists, dermatologists, oral medicine specialists,neurologists and gastroenterologists, who will reach a consensus, when plausible,to the above-mentioned challenges.

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Declaration of Competing Interest

None.

Data availability

No data was used for the research described in the article.

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