
Adherence to treatment in Behçet's syndrome: a multi-faceted issue

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ABSTRACT

Objective. *The aim of this study is to explore the adherence to treatment in patients with Behçet's syndrome (BS), to identify the diverse adherence profiles and their correlations.*

Methods. *A cross-sectional study among adult BS patients was conducted administering an ad-hoc questionnaire to BS patients with the aim of investigating several dimensions related to BS management, including attitudes towards treatment. A Latent Class Analysis (LCA) was performed to identify adherence profiles and associated characteristics were identified using logistic regression analysis.*

Results. *A total of 207 patients answered the survey and 180 of them declared to take medication for BS, thus representing the study population. More than a third of the respondents have declared that they have skipped treatments before and autonomously modified (reduced or increased) the dosage of the treatment without medical consultation. LCA analysis allowed the identification of two distinct profiles, one more stick with recommended medication and the other less adherent to treatment. The less-adherent BS patient profile seems to be related with being in the third decade of life, being diagnosed with BS for more than 5 years and perceiving greater psychological impact of the disease.*

Conclusion. *Addressing adherence in BS is not only related to measuring treatment adherence and identifying the barriers and the limitations; in fact, it should also encompass a wider approach that includes the awareness, the socio-psychological impact of the disease as well as patient education.*

Introduction

Behçet's syndrome (BS) is a chronic autoimmune disease with multisystem involvement, including systematic altera-

tions affecting eyes, vascular tissues and the nervous system, with possible life-threatening consequences (1-3). Accordingly, the therapeutic approach of BS largely depends on the type and the severity of symptoms; several factors can influence the prognosis, also in the long term (4, 5). Among these, adherence to medication can significantly impact the efficacy of the therapeutic approach. Identifying the components associated with low adherence rate could help both physicians and patients to overcome the main barriers to non- or low adherence and therefore, by implementing suitable strategies and initiatives (6).

Despite its importance, adherence to treatment is relatively low investigated in the realm of inflammatory and autoimmune diseases, adding an extra layer of complexity to the management of daily activities for healthcare providers. The World Health Organisation (WHO) defined medication adherence as the extent to which a person – taking medication, following a diet, or executing lifestyle changes – follows medical instructions. As reported by WHO, only one out of two patients with a chronic disease seems to be adherent to treatment in developed countries (7).

In the last two decades extensive research activities have been conducted to address the reasons that govern a lack of adherence. However, medication adherence is still an unresolved problem within the boundaries of public health management, given its high economic and social burden.

Difficulties in adherence to treatments can be influenced both from the side of the patient and from the side of the healthcare providers, also due to the limitations in effectively monitoring patients' behaviours (8).

The conventional way of studying adherence is measuring the reported percentage, as a direct or indirect method, of the prescribed medications doses

taken by the patient over a period of time, and then classifying patients into groups of adherents *versus* non-adherents, typically using arbitrary cut-off values of single indicators of adherence (9).

Since medication non-adherence is a complex phenomenon, the use of tailored questionnaires able to capture several factors like behaviours or attitudes, family, and social support, could offer a worth source of information for those who have to deal with the medication adherence management.

Considering that there are few data on treatment adherence in BS (10, 11), this study aimed to further explore low- or non-adherence in BS. In particular, an *ad-hoc* questionnaire was co-designed with patients affected by BS and launched across the Italian community of BS patients.

The specific objectives of the study were i) the identification of possible subgroups of the study population showing different profiles of adherence based on the variables collected with a dedicated questionnaire administered to BS patients, and using an appropriate multivariate statistical method; ii) assessment of potential patient's personal characteristics associated with the adherence profiles.

Methods

Study design and target population

A cross-sectional study was conducted using an ad-hoc developed questionnaire whose general aim was to investigate several dimensions related to BS and its management, as well as factors related to attitudes towards the treatment that could be related to medication adherence among adult BS patients in Italy.

Measures

The questionnaire was co-designed by clinicians, experts in the management of BS, health economics experts and patients, in collaboration with the Italian patients' association for Behçet's disease (SIMBA OdV). The questionnaire was implemented online using EUSurvey (12) and promoted among Italian BS patients through different dissemination channels with the support

Table I. Main characteristics of the study population (n=180).

		Num. Subj. (%)
Gender	Female	118 (65.6)
	Male	62 (34.4)
Age	18-20 years	8 (4.4)
	21-30 years	22 (12.2)
	31-40 years	61 (33.9)
	41-50 years	62 (34.4)
	51-60 years	23 (12.8)
	61-70 years	4 (2.2)
Marital status	Single	53 (29.4)
	Married	85 (47.2)
	Cohabitant	24 (13.3)
	Divorced	17 (9.4)
	Widow	1 (0.6)
Education	None	1 (0.6)
	Secondary school diploma	31 (17.2)
	High school diploma	94 (52.2)
	Degree	36 (20)
	Post-graduate degree	18 (10)
Working condition	Housewife	10 (5.6)
	Unemployed	20 (11.1)
	Unable to work	14 (7.8)
	Retired	9 (5)
	Student	14 (7.8)
	Employed	113 (62.8)
Full-time/part-time worker	Part-time	33 (29.2)
	Full time	80 (70.8)
Need to change working life	No	60 (33.3)
	Yes	120 (66.7)
Time since diagnosis	<1 year	23 (12.8)
	1-5 years	56 (31.1)
	6-10 years	36 (20)
	11-15 years	26 (14.4)
	16-20 years	16 (8.9)
	≥21	23 (12.8)
Age at first symptoms	0-10 years	32 (17.8)
	11-20 years	46 (25.6)
	21-30 years	49 (27.2)
	31-40 years	40 (22.2)
	41-50 years	11 (6.7)
	51-60 years	1 (0.6)

of SIMBA OdV that disseminated the questionnaire on its website, on the Facebook pages and on other media. Participation to the questionnaire was voluntary and anonymous and they were asked for their consent to analyse their anonymous answers for research purpose (a specific approval was asked in the introduction text of the survey). Since the approach adopted was to fill an anonymous survey with a clear statement of consent filled by the patients, the IRB was not requested. Six domains were investigated: socio-demographic, quality of life, pain, medication adherence, fatigue and disease perception using both open questions and Likert-

scale questions. In the domain of medication adherence, patients were asked about ongoing treatment, if any, and facts describing patients' attitudes towards the treatment: *e.g.* the habit of autonomously skipping therapy, changing dosages without telling the doctor, as well as specific barriers in following the treatment (*i.e.* difficulty in remembering medications to take, difficulty in accessing it due to cost, etc.). Also, possible solutions (*i.e.* better education, use of devices) to improve adherence were assessed.

Statistical analysis

Based on variables collected about pa-

Table II. Characteristics related to on-going treatment and treatment attitudes.

		Num. Subj. (%)
Use of biologics	No	101 (56.1)
	Yes	79 (43.9)
Number of drugs used	≤3	115 (63.9)
	>3	65 (26.1)
Have you ever decided on your own to skip treatment for BS?	Never	115 (63.9)
	Seldom	34 (18.9)
	Sometimes	24 (13.3)
	Often	6 (3.3)
	Always	1 (0.6)
Have you reduced or increased the dose of a BS medication without telling your doctor?	Never	121 (67.2)
	Seldom	25 (13.9)
	Sometimes	23 (12.8)
	Often	9 (5)
	Always	2 (1.1)
You have difficulty remembering all the medicines you have to take?	Never	82 (45.6)
	Seldom	44 (24.4)
	Sometimes	36 (20)
	Often	17 (9.4)
	Always	1 (0.6)
Has the cost of a drug or supplement ever prevented or limited you from following treatment for BS?	Never	100 (55.6)
	Seldom	28 (15.6)
	Sometimes	32 (17.8)
	Often	15 (8.3)
	Always	5 (2.8)
Have you ever forgotten to take your BS medication with you when you travel?	Never	119 (66.1)
	Seldom	33 (18.3)
	Sometimes	17 (9.4)
	Often	5 (2.8)
	Always	6 (3.3)
Do you think that having devices to remind you to take your BS medication could help you to take your treatment more accurately?	No	32 (17.8)
	Yes	108 (60)
	I don't know	40 (22.2)
Are you alone in managing your BS therapy or does someone in your family help you?	No, others help me	54 (30)
	Yes, I'm alone	126 (70)
Do you think the specialist has given you enough information about your BS treatment?	No	36 (20)
	Yes	144 (80)
Have you ever had to discontinue a BS drug after having an unwanted reaction/effect?	No	79 (43.9)
	Yes	101 (56.1)
Do you think that being educated about drugs you take for BS would help you to better manage your therapy?	No	49 (27.2)
	Yes	131 (72.8)

BS: Behçet's syndrome.

tient's adherence, latent class analysis (LCA) was used to identify subgroups of the study population representing different (unmeasured) types of attitudes towards treatment. LCA is a statistical unsupervised model-based technique that allows revealing unobserved heterogeneity and latent structures in a population to find substantially significant groups of people exhibiting similar responses to the measured variables and probabilistically assigning each individual to a class (13, 14).

Estimation in LCA is performed using the maximum likelihood approach and, as in other model-based techniques, fit statistics could be used to assess the model and to choose the most appropriate solution, *i.e.* the optimal number of classes.

In the present analysis the fit of up to five models (one to five classes) was assessed using the Bayesian Information Criterion (BIC) and the Akaike Information Criteria (AIC). The optimal solution corresponded to two classes

and was identified as the one showing the lower BIC and AIC values, together with the best accuracy of classification based on the inspection of average posterior probability of class membership. Based on the solution chosen individuals' class membership was determined on the basis of the model values.

Considering the two-class identified with LCA, logistic regression analysis was used to identify individual characteristics, disease-related variables, factors related to both BS and the treatment, as well as issues that could represent barriers for adherence (*i.e.* drug costs), associated with the likelihood of belonging to one class *versus* the other. Based on variables resulted as significant at simple logistic regression analysis, and after checking collinearity on the basis of the variance inflation factor, a multiple logistic regression model was developed via stepwise bootstrap (considering 1,000 replications).

All analyses were conducted using R version 4.0.4 (15) and LCA was conducted using the poLCA package (16).

Results

A total of 207 BS patients answered the survey and 180 of them declared to take medication for BS, thus representing the study population considered in the present analysis.

Patients included in the study were mainly female (65.6%), aged between 31 and 50 years (68.3%), and almost half of them being married (47.2%). Less than half of the study population was diagnosed with BS within the previous five years (43.9%); an additional 20% of patients were diagnosed between six to ten years from the onset, while the remaining patients had longer history of disease. Further details about patients' characteristics are shown in Table I.

With respect to treatment, less than half of patients (43.9%) declared to receive use biologics and the majority (63.9%) use at least three drugs. Detailed information about treatment and treatment attitudes are reported in Table II. In details, the majority of patients (63.9%) declared they never skipped treatment, and just a small proportion of patients voluntarily decided to not take BS

Table III. Characteristics of the two classes exhibiting different attitudes towards treatment identified based on variables considered in the LCA.

		CL1 (n=114) Num. Subj. (%)	CL2 (n=66) Num. Subj. (%)
Have you ever decided on your own to skip treatment for BS?	Never	107 (93.9)	8 (12.1)
	Seldom	0	27 (40.9)
	Sometimes	0	24 (36.4)
	Often	0	6 (9.1)
	Always	0	1 (1.5)
Have you reduced or increased the dose of a BS' medication without telling your doctor?	Never	96 (84.2)	25 (37.9)
	Seldom	9 (7.9)	16 (24.2)
	Sometimes	7 (6.1)	16 (24.2)
	Often	2 (1.8)	7 (10.6)
	Always	0	2 (3)
You have difficulty remembering all the medicines you have to take?	Never	68 (59.6)	14 (21.2)
	Seldom	27 (23.7)	17 (25.8)
	Sometimes	9 (7.9)	27 (40.9)
	Often	10 (8.8)	7 (10.6)
	Always	0	1 (1.5)
Have you ever forgotten to take your BS medication with you when you travel?	Never	96 (84.2)	23 (34.8)
	Seldom	11 (9.6)	22 (33.3)
	Sometimes	5 (4.4)	12 (18.2)
	Often	2 (1.8)	3 (4.5)
	Always	0	6 (9.1)
Have you ever had to discontinue a BS drug after having an unwanted reaction/effect?	No	65 (57)	14 (21.2)
	Yes	49 (43)	52 (78.8)

BS: Behçet's syndrome.

medications treatment "sometimes" (13.3%) or more frequently (3.9%). Results were quite similar for the variation of the recommended dosage without telling the doctors (about 6.1% did it "often" or "always"); difficulties to remember all the medicines (10% answered "sometimes" or "always") or to forget them when travelling (6.1% answered "sometimes" or "always") emerged just in a minority of patients. Seventy per cent of patients manage their BS therapy by themselves and 80% felt their specialist gave them enough information about BS treatment. The cost of medication was never perceived as a barrier for 55.6% of patients. Almost 60% of the patients perceived as useful having a device to remember medication, and 72.8% highlighted the importance of proper education to better manage their therapy. Results from the LCA revealed the presence of two classes with distinct attitudes toward the treatment. One more committed to stick with the recommended therapy (CL1), representing the larger part of the study group (63.3%), and the second one, less adherent to the treatment recommendation (CL2). Details about the two-class identified

based on the variables considered in the LCA are shown in Table III.

With respect to variables associated with the two classes identified, results from the simple logistic regression models suggested that age, time since diagnosis, the impact of health state on mood, memory problems, the cost of BS treatment, the ability of the therapy to take BS under control, feeling ashamed about the disease and the degree of acceptance of BS are associated with the likelihood of belonging to one of the classes identified (Supplementary Table S1).

Indeed, the multiple logistic regression model showed that the characteristics independently and positively associated with the likelihood of belonging to less adherent class (CL2) are: age in the 31-40 years range, having been diagnosed from more than 5 years, perceiving (always) the impact of the health state on mood, and been ashamed (often/always) about BS. On the other hand, a negative association with the likelihood of belonging to less adherent class (CL2) was found for both the perception of a little ability of the therapy to keep BS under control (*vs* not at all) and the complete ability of the therapy to keep BS under control (see Table IV).

Discussion

In this study we investigated adherence to treatment in BS patients, focusing on specific profiles of patients that might be associated with low or non-adherence.

First of all, the results from the present study highlighted two subgroups of the study population with distinct attitudes towards the treatment, one stick to the prescribed medication and the other one less adherent. Notably, the first group is the most represented. This prevailing attitude towards the treatment could be explained by the high importance of education recognised among the study population and the good satisfaction with education received. Indeed, 80% of respondents have received good level of information about the treatment from their clinicians, almost 73% of BS patients believe that being educated on the treatment would help them to better manage their therapy. Proper education is fundamental to induce patients' empowerment and also to improve medication adherence, and our findings bring further evidence to the importance of therapeutic education in improving adherence to treatment and the overall management of the disease. Besides education related to pharma-

Table IV. Results from the multiple logistic regression model used to evaluate association with the likelihood of belonging to CL2, the "less adherent" class.

		OR (95%CI)	p-value
Age	18-30 years	(ref.)	
	31-40 years	4.211 (1.322-14.984)	0.019
	41-50 years	1.763 (0.560-6.021)	0.344
	>50 years	1.350 (0.330-5.659)	0.676
Time since diagnosis	< 1 years	(ref.)	
	1-5 years	6.757 (1.643-38.827)	0.015
	6-10 years	8.716 (1.829-55.566)	0.011
	11-15 years	7.524 (1.565-47.917)	0.018
	>15 years	8.793 (1.965-53.308)	0.008
Does your state of health affect your mood?	Never/Rarely	(ref.)	
	Sometimes	5.630 (1.135-44.337)	0.055
	Often	4.252 (0.845-33.630)	0.110
	Always	6.245 (1.168-51.381)	0.049
Is the therapy you are taking keeping your illness under control?	1-Not at all	(ref.)	
		0.124 (0.013-0.926)	0.048
		0.279 (0.033-1.893)	0.204
	5-Completely	0.149 (0.016-1.098)	0.071
		0.053 (0.004-0.491)	0.013
Do you feel ashamed of your illness?	Never	(ref.)	
	Rarely	2.473 (0.893-6.996)	0.083
	Sometimes	1.314 (0.521-3.295)	0.560
	Often/Always	6.400 (2.203-20.103)	0.001

BS: Behçet's syndrome.

covigilance, it seems clear that BS patient are keen on receiving therapeutic education.

Interestingly, findings from the LCA analysis also allowed the identification of a profile of BS patient that is less adherent to treatment (CL2).

In detail, despite the high prevalence of adherent attitudes more than a third of the respondents have declared they have skipped treatments or autonomously modified the dosage of the treatment without medical consultation. Fifty-six per cent of BS patients have discontinued their treatment due to reaction/effect symptoms they attributed to the treatment. Future research activities should be addressed to collect additional clinical data to disentangle drug adverse reactions from symptoms due to BS itself or to other concomitant conditions. Also, a deeper characterisation of the type of treatment discontinued (e.g. on-vs off-label drugs) might provide useful elements for healthcare providers. Indeed, given the complexity of clinical features in BS, a wider comprehension of adherence dynamics can contribute to an efficient management of the disease from both patient's and healthcare professionals' perspective (17).

Moreover, even if two thirds of the respondents have reported that they have never skipped the treatment, 54% find it difficult remembering to take their medication and 60% of respondents have declared that having a device to remind their treatments would help them in being more adherent to the prescription. This might be easily related also to the fact that many BS patients are prescribed different medications and it is confirmed by our respondents that in most cases, they are taking more than three different treatments.

Notably, findings from the present study also allow the identification of variables associated with non-adherent attitudes thus supporting the identification of patients' profile that could be more exposed to non-adherence also informing the development of appropriate strategies.

In details, the less-adherent BS patient profile seems to be related with being in the third decade of life and to being diagnosed with BS for more than 5 years. In addition, it seems that being diagnosed for a long period of time increases the chances of being less adherent to treatment. Actually, our results seem to be aligned with what is usually observed in routine clinical practice,

in which BS patients with a long history of disease have demonstrated, on one hand to be able to manage more effectively their disease, and on the other hand, also tend to be prone to modify their treatment without clinical consultation. This might suggest, on the one hand, the attitude of the long-term patient who feels able to manage the treatment independently, perhaps adapting it in relation to the phases of the illness, or contrarily, on the other hand, the need to undertake educational or other interventions in long-term patients in order to avoid attitudes of non-adherence.

Another relevant result is related to how BS patients perceive their treatment as efficacious in keeping their disease under control. A significant proportion of the less-adherent BS patients perceives that the treatment is keeping the disease completely under control; apparently, this result seems to be conflicting with the less-adherence profile, since it is expected that being non-adherent has a direct impact on the drug efficacy and therefore on the control of the disease. However, our main hypothesis is that a lower adherence in BS can be related to how the patient perceives the efficacy of the treatment. In particular,

two main scenarios could be identified: the first scenario could be represented by a BS patient who does not perceive a significant response to the treatment and, for this reason, tends to be more adherent to the prescription in order to "increase" the chance of being responsive to the therapy. The second scenario may include a patient that perceives the full efficacy of the treatment on the diseases and tends to be less adherent to the treatment, with the "consciousness" that, if needed, the treatment will be effective and, in this way, there is a lower need of being fully adherent with the prescription. Nevertheless, we should also take into consideration that several reasons could be responsible of low- or non-adherence, such as the relapsing-remitting course of BS and ongoing activity despite treatment.

Finally, beyond the issues strictly related to the perception and the management of the treatment *per se*, another crucial aspect of adherence that also needs to be taken into account is the psychological impact of the disease on BS patients. In fact, the less adherent profile seems to perceive that their health status highly affects their mood and that they often/always feel ashamed of having BS. The possible influence that the psychological burden related to the disease can have on adherence to treatment represents a crucial dimension that would definitely need to be explored in further BS studies.

Although the main limitation of the study might seem to be represented by the use of a non-validated questionnaire, we think that the main strength of this study is to have adopted a participatory approach to design the questionnaire. All the questions were indeed co-designed with a panel of BS patients, allowing the identification of the most relevant issues from both patients' and clinicians' point of view.

The self-selected nature of the study sample and desirability bias represented additional limitation of the current study. Despite these caveats, our study represents the first nation-wide study that addressed adherence to treatment in BS that were treated in different centres and belonged to the Italian community of BS patients; the present study also adds

to the limited evidence that has studied adherence by considering an approach tailored to assess the multidimensional nature of the phenomenon (18).

Conclusions

Low or non-adherence to treatment in BS is a multifaceted issue that need to be addressed with a multi-dimensional and participatory approach. Therefore, addressing adherence in BS is not only related to measuring adherence to medication, and its barriers, but should consider patient's awareness, and the perceived socio-psychological burden of the disease. Future therapeutic strategies might focus on patient education and patient involvement both in clinical and research contexts.

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Authors' contributions

R. Talarico, D. Marinello and V. Lorenzoni conceived the paper; V. Lorenzoni and G. Androzzini performed the statistical analyses; S. Pirri, V. Lorenzoni and D. Marinello wrote the manuscript. All the authors were involved in study design, discussion, and interpretation of the results. All the authors repeatedly edited the manuscript and approved the final version.

Key messages

- Medication adherence is still an unresolved problem within the boundaries of public health management, given its high economic and social burden.
- The added value of this study was the novel co-designing approach to the problem, performed with BS patients.
- The identification of two main adherence profiles and associated characteristics represent relevant basis for future investigations.

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