ORIGINAL ARTICLE

Treatment Patterns and Clinical Outcomes of Chronic Urticaria: Two-year Follow-up Results from the Scandinavian AWARE Study

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The AWARE (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) study investigated outcomes in patients with chronic urticaria refractory to H1-antihistamine. The objective of the current study was to analyse the effects of treatment on patients' symptoms and quality of life for a period of up to 2 years. Over the 2 years, there was clear improvement in the high rates of disease burden from baseline, as evidenced by lower scores for disease severity scales, better quality of life, and a decreasing rate of medical resource utilization. However, this is the result of treatment adherence to the guidelines in highly specialized Scandinavian urticaria centres, and has its basis in the relatively low treatment intensity and control at enrolment. There is a need for greater adherence to the treatment guidelines and better management of antihistamine-refractory chronic urticaria.

Key words: chronic urticaria; quality of life; patient-reported outcomes; omalizumab; AWARE.

Accepted Feb 15, 2022; Epub ahead of print Feb 15, 2022

Acta Derm Venereol 2022; 102: adv00689.

DOI: 10.2340/actadv.v102.1620

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SIGNIFICANCE

The AWARE (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) study investigated outcomes in patients with chronic urticaria refractory to H1-antihistamine. The objective of this study was to analyse the effects of treatment on patients' symptoms and quality of life for a period of up to 2 years. Over the 2 years, there was clear improvement in the high rates of disease burden from baseline, as evidenced by lower scores for disease severity scales, better quality of life, and a decreasing rate of medical resource utilization. However, this is the result of treatment adherence to the guidelines in highly specialized Scandinavian urticaria centres, and has its basis in the relatively low treatment intensity and control at enrolment. There is a need for greater adherence to the treatment guidelines and better management of antihistamine-refractory chronic urticaria.

Urticaria is defined as the sudden development of transient hives (wheals) and/or angioedema, and has a lifetime prevalence of approximately 20% (1). Chronic urticaria (CU) affects approximately 1% of the general population and is characterized by the recurrence of hives (wheals) and/or angioedema for longer than 6 weeks. CU can be divided based on whether the disease occurs spontaneously (chronic spontaneous urticaria; CSU), or with an external trigger (chronic inducible urticaria; CIndU) (2, 3). Although the exact pathogenesis is not known, CSU is considered to be a mast cell-driven skin disease and autoimmunity is thought to be its most frequent cause (4, 5). On the other hand, specific triggers, such as heat, cold, and pressure, are features of CIndU (2, 6–9). Irrespective of the origin of the symptoms, CU results in serious impairment in quality of life (QoL) and negatively affects daily activities. It influences the socio-psychological status of an individual and results in low self-esteem (10–14). The sudden and unpredictable appearance of symptoms and associated discomfort often results in depression and other frustration (15). Hence, along with management of the symptoms, management of the psychological state of the patient and improvement in QoL form an integral part of CU treatment.

Second-generation H1-antihistamines at the locally approved dose are recommended as the first-line therapy by the EAACI/GA²LEN/EDF/WAO guidelines. In unresponsive patients this is followed by second-generation H1-antihistamines at up to 4× the approved dose as second-line therapy (3). Omalizumab is recommended as add-on third-line therapy to H1-antihistamines; followed by cyclosporine if further escalation is needed and oral corticosteroids are prescribed for acute exacerbations (3, 16). Detailed guidelines for the management of CSU are available; however, adherence to these guidelines in real-world clinical practice may not have been adequate. Hence, there is a need to understand trends in clinical management and outcomes of CSU to understand the status of adherence to these guidelines in Scandinavian countries.

The AWARE (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) study, under conditions of daily living, evaluated disease burden, current treatment schedule, and clinical resources use of patients

with H1-antihistamine-refractory CU as a function of their administered therapy (10). The study was designed to describe the diagnosis and subsequent management of CU, as well as determine the impact of the treatment chosen by the physician on the patient's QoL in a real-world setting. The CU scenario in the Scandinavian countries in not clear, due to the lack of any specific registry, and similarly the treatment patterns in the clinical settings are largely unknown.

The data from the AWARE study specific to Denmark, Sweden and Norway was analysed to describe the burden of the disease, as well as the consequences of the same in this patient population. The aim was also to understand the effects of treatment on patients' symptoms and QoL. The current paper reports the 2-year final findings of this study from the Scandinavian population.

MATERIALS AND METHODS

AWARE is a multicentre, global and prospective observational study conducted in the USA, Latin America, Canada and 12 European countries, including Denmark, Sweden and Norway (7 study centres and 161 patients). This study was conducted in accordance with the Declaration of Helsinki, the principles of Good Clinical Practice, and national laws and regulations regarding clinical studies. Approval from the Institutional Review Board/Independent Ethics Committee/Research Ethics Board was obtained for each centre, and all participating patients gave written informed consent before any data were recorded.

To be eligible for participation in the study, the patients had to be ≥18 years with a medically confirmed diagnosis of CU for more than 2 months, which was refractory to treatment with H1-antihistamines (refractory disease was defined as evidence of failed labelled dose or up to 4-fold labelled dose of H1-antihistamines). Patients participating in any other clinical urticaria study were excluded from the study. Patients were also excluded if it was unlikely they would be available for the full duration of the observational period of 24 months. For a period of 2 years, therapeutic effects in terms of symptom control and QoL improvement were recorded. It must be noted that the results of the current trial may be helpful in forming the evidentiary foundation to design further real-world registries for CSU in Scandinavia.

The primary objective of the worldwide AWARE study was to associate patient-reported outcomes (PROs: Dermatology Life Quality Index, DLQI; Chronic Urticaria Quality of Life questionnaire, CU-Q2oL; CU specific Work Productivity and Activity Impairment, WPAI-CU; Urticaria Control Test, UCT and optional Urticaria Activity Score over 7 days, UAS7) with the treatment options used in patients with H1-antihistamine-refractory CU. Patient satisfaction with the current therapy was measured by visual analogue scale (VAS), where 0=not at all satisfied to 10=very satisfied. The disease burden, (including impact on sleep and work productivity), comorbidities of patients with refractory CU (including asthma, allergic rhinitis, atopic dermatitis, eczema, nut allergy, depression, anxiety disorders, Hashimoto thyroiditis, type 1 diabetes, vitiligo, lupus erythematosus, obesity, hypertension, hypertriglyceridemia) as well as the previous and current medications were documented. The study further determined the standard of care and assessed the utilization of medical facilities (hospitalizations, frequency of practice visits); treatment algorithms and trends during the study course (including therapy adjustments and duration of use of the respective substance class) were described.

RESULTS

The baseline characteristics of the patients enrolled from Denmark, Sweden and Norway have been described previously (17). In total, 161 patients were registered from specialized urticaria centres across Norway (n=50), Sweden (n=28) and Denmark (n=3), of which 158 CU patients met the eligibility criteria and were enrolled in the study. Premature withdrawal was observed for 27 patients (16.9%). The most frequent reason for discontinuation was withdrawal of informed consent (n=12, 44.4% of patients with discontinuation), followed by lost to follow-up (n=10, 37.0% of patients with discontinuation) and spontaneous remission of CU (n=5, 18.5% of patients with discontinuation). The mean patient age was 40.4 years, and the majority of patients were female (70%). CSU was the most frequent diagnosis (61.4%); 20.2% patients had both CSU and CIndU; while 18.4% had CIndU only (**Table I**).

Pharmacological treatment

At enrolment, only 61.9% of all patients received prior medication, whereas 99.4% of all patients were treated with medication during the study period. Approximately 50% of the patients did not receive omalizumab at all through the study (**Table II**). During the course of the study, montelukast was prescribed to 14.0% of the patients. Monotherapy with ciclosporin was rarely used, with only 1 patient receiving it at enrolment and at 2 years. No clear differences were observed in the prescription of urticaria medication between men and women. Of all 108 patients who took omalizumab at least once, 42.6% were continuously treated with omalizumab prior and during the course of the study (**Table III**). The most predominant monthly dosage of omalizumab was 300–450 mg (76.9%; covering the actually approved dosage of 300

Table I. Baseline disease and demographic characteristics

Characteristics	
Age, years, mean (SD)	40.4 (13.5)
<25 years, *n* (%)	20 (12.5)
25–<35 years, *n* (%)	37 (23.1)
35–<45 years, *n* (%)	42 (26.3)
45–<55 years, *n* (%)	34 (21.3)
55–<65 years, *n* (%)	19 (11.9)
65–<75 years, *n* (%)	8 (5.0)
≥75 years, *n* (%)	0 (0.0)
Female	112 (70)
Body mass index, kg/m^2, mean (SD)	26.6 (5.1)
≤18.5 (underweight), *n* (%)	1 (0.6)
>18.5 to ≤25 (normal weight), *n* (%)	68 (42.5)
>25 to ≤30 (over-weight), *n* (%)	58 (36.3)
>30 to ≤40 (adiposity), *n* (%)	29 (18.1)
>40 (extreme adiposity), *n* (%)	4 (2.5)
Chronic spontaneous urticaria, *n* (%)	98 (61.3)
Induced urticaria, *n* (%)	29 (18.1)
Both, *n* (%)	33 (20.6)
Duration of disease, years, mean (SD)	6.4 (8.4)
Family-related history of urticaria, *n* (%)	14 (8.8)

SD: standard deviation.

Table II. Treatment prescribed at enrolment and at 2 years after enrolment

Medication	Prior to enrolment *n* = 160 *n* (%)	At enrolment *n* = 160 *n* (%)	At 2 years after enrolment (*n* = 102) *n* (%)
Any treatment	99 (61.9)	159 (99.4)	98 (96.1)
nsH1-AH approved	9 (5.6)	4 (2.5)	6 (5.9)
Up-dosed nsH1-AH	30 (18.8)	32 (20.0)	30 (29.4)
On demand nsH1-AH	3 (1.9)	0 (0.0)	4 (3.9)
sH1-AH	3 (1.9)	0 (0.0)	0 (0.0)
Combination nsH1-AH and sH1-AH	1 (0.6)	0 (0.0)	0 (0.0)
Omalizumab	12 (7.5)	104 (65.0)	50 (49.0)
Montelukast	19 (11.9)	17 (10.6)	7 (6.9)
Ciclosporin	3 (1.9)	1 (0.6)	1 (1.0)
Other	19 (11.9)	1 (0.6)	0 (0.0)
No treatment	61 (38.1)	1 (0.6)	4 (3.9)

nsH1-AH: non-sedating H1-antihistamines; sH1-AH: sedating H1-antihistamines.

mg), followed by 150–300 mg and 450–600 mg (8.3% for both). Corticosteroids were used by 31 (19.4%) of patients as prior therapy, 33 (20.6%) as current therapy at baseline, and 14 (13.7%) at year 2 of the study.

Burden of disease: disease activity, quality of life and work productivity

The frequency of recurrent wheals or wheals during the last 12 weeks decreased from 70.9% (4 months) to 54.5% (2 years) and the occurrence of angioedema decreased from 17.4% to 7.1%. At baseline, 71.1% of enrolled CU patients showed poor control (UCT <12), with a mean UCT of 8.3 (4.8). The condition steadily improved at 1 year and 2 years, with a mean UCT of 11.5 (4.1) and 12.1 (3.9), respectively (**Fig. 1**). For the treatment group on up-dosed non-sedating H1-antihistamines the frequency of patients with poor urticaria control (UCT total score <12) decreased from 56.7% at enrolment to 42.4% at 4 months and thereafter remained fairly constant over time (at 2 years: 41.7%). However, previous omalizumab therapy was associated with a high proportion of controlled urticaria patients, ranging from 41.7% at enrolment to 83.0% at 2 years. Similarly to UCT an improvement

Table III. Omalizumab therapy by diagnosis

Treatment	CSU *n* = 98 *n* (%)	CindU *n* = 29 *n* (%)	CSU + CindU *n* = 33 *n* (%)	Total *n* = 168 *n* (%)
Continuous omalizumab treatment	33 (48.5)	6 (28.6)	7 (36.8)	46 (42.6)
Prior omalizumab treatment	3 (4.4)	0	0	3 (2.8)
Omalizumab started during the study	9 (13.2)	8 (38.1)	4 (21.1)	21 (19.4)
Other omalizumab treatment dosings[a]	23(33.8)	7 (33.3)	8 (42.1)	38 (35.2)
Dosage				
<150 mg	3 (4.4)	0 (0.0)	1 (5.3)	4 (3.7)
150–<300 mg	7 (10.3)	1 (4.8)	1 (5.3)	9 (8.3)
300–<450 mg	50 (73.5)	17 (81.0)	16 (84.2)	83 (76.9)
450– ≤600 mg	6 (8.8)	3 (14.3)	0 (0.0)	9 (8.3)
>600 mg	2 (2.9)	0 (0.0)	1 (5.3)	3 (2.8)

[a]Patients who took omalizumab at any time during the study (e.g. interruption of treatment).
CSU: chronic spontaneous urticaria; CindU: chronic inducible urticaria.

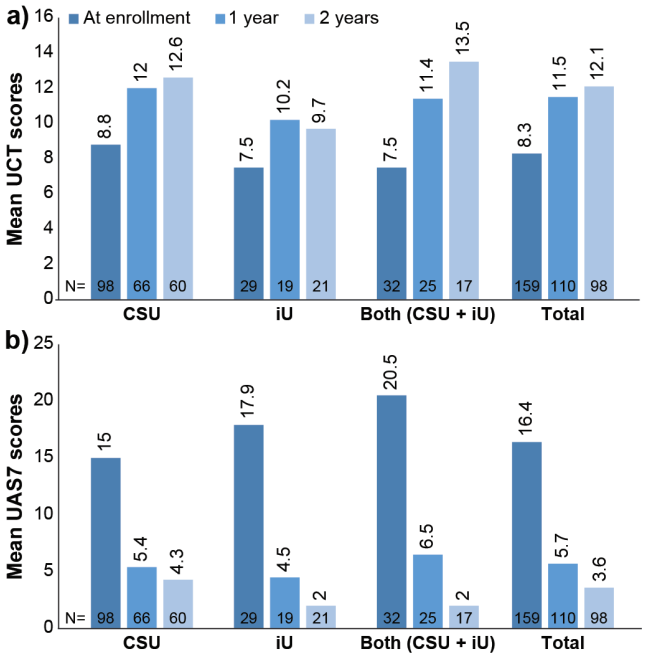

Fig. 1. Clinical outcomes from enrolment up to 2 years of follow-up. Mean UAS7 is not a standard assessment for patients with only chronic inducible urticaria, and, hence, not presented in (b). CSU: chronic spontaneous urticaria; iU: chronic inducible urticaria; UAS7: urticaria activity score over 7 days; UCT: urticaria control test.

in UAS7 scores were noted from 16.4 (11.4) at baseline to 3.6 (4.8) at 2 years, indicating decrease in the activity of the disease.

The overall effect of CU on QoL decreased as the patients received treatment, with mean DLQI total scores decreasing from 7.3 (6.3) at enrolment to 4.1 (5.0) at 2 years. At baseline, only 23.7% of the patients assessed CU as having no impact on their QoL at baseline, this percentage increased to 44.3% at 1 year, and 46.4% after 2 years. For all DLQI sub-scores, an improvement in QoL was observed during the course of the study. The CU-Q2oL was only assessed in Denmark. The mean CU-Q2oL score decreased from 29.6 (21.4) at enrolment to 12.2 (10.9) at 2 years, indicating a clear improvement in the patients' QoL over the period of 2 years studied. Also, meaningful decreases during the course of the study were observed in all CU-Q2oL sub-scores (functioning, sleep, itching embarrassment, mental status, swelling/eating, limit looks). Mean VAS values increased during the study period from 6.1 to 7.5, indicating a higher satisfaction with the current treatment. The mean percentage of total work productivity impairment by urticaria decreased from 23.2% (visit 1) to 14.3% at 1 year and 12.0% at 2 years (**Table IV**). Similarly, the patient's mean ability to perform regular daily activities was impaired in approximately one-third at baseline (29.3%). This impairment decreased during the first year of the study (17.5% at year 1) with a further slight decrease at year 2 (12.5%). Only 11.4% of the patients were on sick leave during enrolment, with a mean duration of 2.5 weeks; this decreased to 2.9% by the end of year 2 (**Fig. 2**).

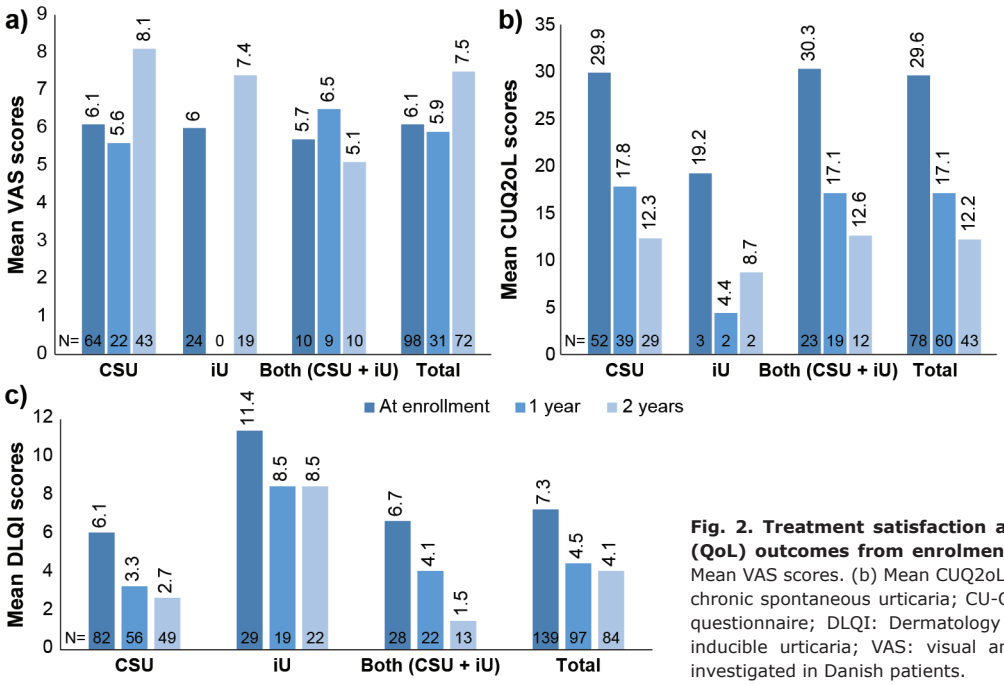

Fig. 2. Treatment satisfaction and health-related quality of life (QoL) outcomes from enrolment up to 2 years of follow-up. (a) Mean VAS scores. (b) Mean CUQ2oL scores. (c) Mean DLQI scores. CSU: chronic spontaneous urticaria; CU-Q2oL: chronic urticaria quality of life questionnaire; DLQI: Dermatology Life Quality Index; CindU: chronic inducible urticaria; VAS: visual analogue score. *CU-Q_2oL was only investigated in Danish patients.

Healthcare resource utilization

Rates of healthcare utilization decreased substantially over the period of 2 years: at enrolment and 2 years, respectively,72.5% vs 68.8% of patients had visited a general practitioner (GP), 68.6% vs 6.3% had visited another dermatologist or allergist, 42.5% vs 12.5% had visited specialized urticaria centres, and 27.5% vs 0% had visited an emergency physician or the emergency room due to urticaria (**Fig. 3**).

DISCUSSION

The primary aim of the AWARE study, to collect real-world evidence on disease burden and treatment modalities in patients with CU, was achieved by enrolling 3,732 patients across 12 European countries (17, 18). The study did not investigate a specific medical product, but assessed how patients with H1-antihistamine-refractory CU were currently treated in different European countries. The data presented here reports on the subpopulation of Scandinavian patients, who showed a high disease burden at baseline, as indicated by considerably decreased QoL, an angioedema rate of 32.5%, and a relatively high medical resource utilization.

This study population comprised 160 patients with CU with various dermatological- and non-dermatological comorbidities, providing an insightful portrayal of the treatment regimens of CU patients in Scandinavia, and allowing for comparison with the overall AWARE population. The rate of patients with pure CindU was higher in this subpopulation (18.1%) than in the overall AWARE population (5.8%) (18). However, demographic characteristics of enrolled patients were largely in line with the published literature, and there was also a strong similarity to the overall AWARE population (18).

Treatment regimens varied widely, yet the recommended treatment options of non-sedating H1-antihistamines at approved and escalated doses were the most frequently prescribed medications. Omalizumab as the only approved treatment for CSU in case of insufficiency of non-sedating H1-antihistamines was prescribed in 65.6% of the patients. The most frequent predominant monthly dosage of omalizumab was either 300 mg or 450 mg (76.9%). It must be noted that there was off-label use of omalizumab treatment of CindU patients, as also the use of omalizumab doses above the approved 300 mg dose in patients with CSU. There was also a decrease in the use of non-recommended treatment options, such as montelukast, and ciclosporin, at 2 years of observation in this study.

During the 2-year observation period, CU patients' disease activity declined markedly, which was reflected in the UAS7 scores over time. Improvements were also

Table IV. Work productivity and activity impairment in patients with chronic urticaria at enrolment and 2 years after enrolment

Outcomes	At enrolment	2 years after enrolment
Work productivity and activity impairment		
Presenteeism, %, mean (SD)	20.6 (22.6)	9.7 (18.8)
Absenteeism, %, mean (SD)	3.7 (11.9)	3.0 (10.9)
Total work productivity impairment, %, mean (SD)	23.2 (24.0)	12.0 (21.6)
Total activity impairment, %, mean (SD)	29.5 (28.3)	12.5 (20.7)
Sick leave		
Sick leave due to urticaria, *n* (%)	41 (25.9)	3 (2.9)
Duration of sick leave, weeks/year, mean (SD)	3.8 (6.3)	NA

NA: not available; SD: standard deviation.

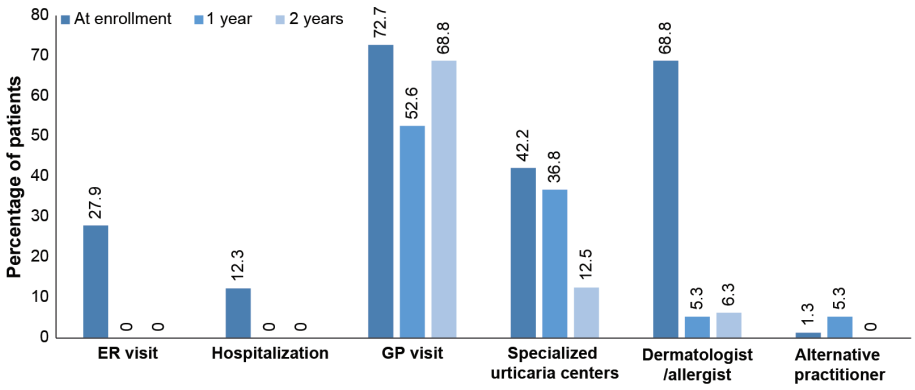

Fig. 3. Healthcare utilization due to urticaria at enrolment and up to 2 years. ER: emergency room; GP: general practitioner.

reflected in QoL according to CU-Q2oL and DLQI. At baseline, only 23.7% of the patients assessed CU as having no impact on their QoL, after 1 year 44.3%, and after 2 years 46.4%. Treatment response was mirrored in the effects of CU on work-life (WPAI-CU): total work productivity impairment decreased markedly over the 2 years. These trends reflect the results from the AWARE study in Germany, where at 2 years of observation, continued treatment was associated with treatment benefits beyond initial management (19). Similarly, the 2-year results from the AWARE study in the Asia, Middle East and Africa regions showed improvements in patient outcomes. Despite the differences in the healthcare systems compared with developing countries, these data suggest that, even in Scandinavian countries, patients continued to improve throughout the treatment period. This suggests that prolonged treatment may be beneficial beyond the initial results, and continued management is essential to obtain maximum benefit of a therapy.

At baseline, patients with CU demonstrated a high rate of medical resource utilization: in many cases, multiple dermatologists/allergists had been consulted, in addition to GP involvement. Hospitalization due to CU was seen in as many as 12.3% of cases, and 26.3% of patients reported sick leave since the onset of disease. Over the course of follow-up, the healthcare utilization decreased substantially, leading to reduced visits to the specialist, emergency rooms as well as the GPs. Nevertheless, CU was still considered less well-controlled after 2 years in many patients, despite receiving specialist care. Recent publications from the AWARE study from Germany, Portugal, and the overall European sample, showed that, despite receiving specialist care, patients across Europe may be experiencing sub-optimal outcomes (18, 19).

As in any non-interventional study, the assessment of real-world practice is also the main limitation of the AWARE study. The current study did not systematically collect tolerability data, thus precluding interpretation of the safety profile of any of the used drugs. There were no pre-defined or randomized group assessments of patients; instead, data describing the treatment strategy of a patient were assessed on an ongoing basis and could also vary during the study. The study, however, provides meaningful insights into real-world treatment patterns and clinical outcomes in the Scandinavian subpopulation, and highlights the need for greater adherence to the treatment guidelines and better management of the disease.

ACKNOWLEDGEMENTS

The authors acknowledge K. M. Ashwini Kumar (Novartis Healthcare Pvt Ltd, India), and Aafrin Khan (Novartis Healthcare Pvt Ltd, India) for editorial and writing support, in accordance with the Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

The study was funded by Novartis Pharma AG.

Conflicts of interest- SFT, ECP, CDA and CV have received research support, consultancy fees and lecture fees from Novartis. SJ and NVB are full-time employees of Novartis Norge AS, Oslo, Norway. RD is a full-time employee of Novartis Pharmaceutical A/S, Copenhagen, Denmark. A-KD is a full-time employee of Novartis Sweden AB, Stockholm, Sweden.

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