CONCISE REPORT

Demographic, clinical and antibody characteristics of patients with digital ulcers in systemic sclerosis: data from the DUO Registry

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ABSTRACT

Objectives The Digital Ulcers Outcome (DUO) Registry was designed to describe the clinical and antibody characteristics, disease course and outcomes of patients with digital ulcers associated with systemic sclerosis (SSc).

Methods The DUO Registry is a European, prospective, multicentre, observational, registry of SSc patients with ongoing digital ulcer disease, irrespective of treatment regimen. Data collected included demographics, SSc duration, SSc subset, internal organ manifestations, autoantibodies, previous and ongoing interventions and complications related to digital ulcers.

Results Up to 19 November 2010 a total of 2439 patients had enrolled into the registry. Most were classified as either limited cutaneous SSc (lcSSc; 52.2%) or diffuse cutaneous SSc (dcSSc; 36.9%). Digital ulcers developed earlier in patients with dcSSc compared with lcSSc. Almost all patients (95.7%) tested positive for antinuclear antibodies, 45.2% for anti-scleroderma-70 and 43.6% for anticientromere antibodies (ACA). The first digital ulcer in the anti-scleroderma-70-positive patient cohort occurred approximately 5 years earlier than the ACA-positive patient group.

Conclusions This study provides data from a large cohort of SSc patients with a history of digital ulcers. The early occurrence and high frequency of digital ulcer complications are especially seen in patients with dcSSc and/or anti-scleroderma-70 antibodies.

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterised by microvascular damage and excessive fibrosis of the skin and various internal organs. Limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) subsets are also associated with the presence of a number of autoantibodies, the expression of which can be useful in the diagnosis, prognosis and SSc disease management.

The European Medicines Agency (EMA) requested the establishment of a prospective registry of patients with ongoing digital ulcers associated with SSc as a licensing requirement for bosentan in this indication. The Digital Ulcers Outcome (DUO) Registry enrolls patients with digital ulcer disease regardless of their treatment status; however, a large proportion are receiving bosentan. This study provides valuable insights into this patient group and here we describe the clinical and autoantibody characteristics of these patients at enrolment.

METHODS

The DUO Registry was initiated in April 2008 as an EMA postapproval commitment (after approval of a new indication for bosentan ‘to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease’). Participating centres received approval from relevant national and local ethics committees, data protection and health authorities. In line with an observational study design, physicians were asked to enter all consenting consecutive patients with ongoing digital ulcers associated with SSc, irrespective of treatment regimen. Patients received standard medical care and follow-up as determined by their physician. Data definitions were informed by literature and scientific committee consensus. Data collection included demographics, SSc disease duration, underlying disease classification (lcSSc, dcSSc, overlap SSc/mixed connective tissue disease and other), internal organ manifestations, autoantibodies, history of interventions/complications related to digital ulcers, ongoing complications related to digital ulcers, and ongoing medications and functional assessment based on a disease-specific questionnaire. The presence of antinuclear antibodies, anti-scleroderma-70 antibodies, anticientromere antibodies (ACA), anti-RNA polymerase 3, anti-U1 ribonucleoprotein and anti-U3 ribonucleoprotein were recorded. All serology tests and other data collection parameters were collected if performed. Quality assurance comprised automatic online quality checks and annual source data verification on 10% of the patients.

Data analysis

Enrolment data for the antibody subsets were analysed cross-sectionally for differences by group. SAS statistical software was used for analysing the data. Descriptive statistics (mean, median, SD, 95% CI, minimum, maximum) were provided for numerical variables. Categorical variables were summarised by counts and percentages and 95% CI.

RESULTS

As of 19 November 2010, a total of 2439 patients had been enrolled into the DUO Registry from 271
Table 1: Demographics and clinical features by antibody status

<table>
<thead>
<tr>
<th>Antibody Subgroup</th>
<th>ANA* (N=2085)</th>
<th>Anti-scl-70 (N=854)</th>
<th>Anti-RNA Pol 3 (N=86)</th>
<th>Anti-U3 RNP (N=39)</th>
<th>ACA (N=775)</th>
<th>Anti-U1 RNP (N=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tested positive/tests performed (%)</td>
<td>2085/2179 (95.7)</td>
<td>854/1888 (45.2)</td>
<td>86/867 (9.9)</td>
<td>775/1778 (43.6)</td>
<td>120/1243 (9.7)</td>
<td>39/799 (4.9)</td>
</tr>
<tr>
<td>Female, n/N (%)</td>
<td>1719/2085 (82.4)</td>
<td>676/854 (79.2)</td>
<td>70/86 (81.4)</td>
<td>677/775 (87.4)</td>
<td>91/120 (75.8)</td>
<td>31/39 (29.5)</td>
</tr>
<tr>
<td>dcSSc, n/N (%) (95% CI)</td>
<td>1071/2070 (51.7) (49.6 to 53.9)</td>
<td>249/848 (29.4) (26.3 to 32.6)</td>
<td>28/85 (32.9) (23.1 to 44.0)</td>
<td>14/54 (25.9) (14.3 to 38.4)</td>
<td>34/119 (28.6) (20.7 to 37.6)</td>
<td>10/38 (26.3) (13.4 to 43.1)</td>
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<tr>
<td>lcSSc, n/N (%) (95% CI)</td>
<td>1071/2070 (51.7) (49.6 to 53.9)</td>
<td>249/848 (29.4) (26.3 to 32.6)</td>
<td>28/85 (32.9) (23.1 to 44.0)</td>
<td>14/54 (25.9) (14.3 to 38.4)</td>
<td>34/119 (28.6) (20.7 to 37.6)</td>
<td>10/38 (26.3) (13.4 to 43.1)</td>
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<tr>
<td>Overlap SSc/mCTD, n/N (%) (95% CI)</td>
<td>149/2070 (7.1) (6.1 to 8.2)</td>
<td>34/848 (4.0) (2.9 to 5.2)</td>
<td>14/85 (16.5) (9.3 to 26.1)</td>
<td>638/770 (82.9) (80.0 to 85.5)</td>
<td>38/119 (31.9) (23.7 to 41.1)</td>
<td>15/38 (39.5) (24.0 to 56.6)</td>
</tr>
<tr>
<td>Time from onset of RP to first digital ulcer, years, mean (95% CI)</td>
<td>6.6 (6.2 to 7.0)</td>
<td>6.0 (5.4 to 6.6)</td>
<td>6.1 (4.4 to 7.8)</td>
<td>8.1 (7.3 to 9.0)</td>
<td>6.5 (4.9 to 8.0)</td>
<td>6.9 (3.5 to 10.4)</td>
</tr>
<tr>
<td>Time from first non-RP to first digital ulcer manifestation, years, mean (95% CI)</td>
<td>3.6 (3.2 to 4.0)</td>
<td>3.2 (2.9 to 3.6)</td>
<td>3.2 (2.9 to 3.6)</td>
<td>3.2 (2.9 to 3.6)</td>
<td>3.2 (2.9 to 3.6)</td>
<td>3.2 (2.9 to 3.6)</td>
</tr>
</tbody>
</table>

The denominator N varies according to the number of available observations.


Clinical and epidemiological research

Study cohort characteristics

The mean age of the patients enrolled was 54.6 years (SD 14.1) and the majority were women. Age at first Raynaud’s phenomenon on average 39.8 years and age at first digital ulcer was 46.7 years. At the time of enrolment, 60.0% (1426/2377) had at least one digital ulcer (data were missing for 62 patients). All patients who had no current digital ulcers at enrolment had a history of digital ulcer disease. Overall, 52.2% of the patients were classified as lcSSc, 36.9% as dcSSc, 6.8% as overlap SSC/mixed connective tissue disease, and 4.1% had other diseases (eg, systemic lupus erythematosus, dermatomyositis, vasculitis or SSC not further specified) (data were missing for 44 patients).

At enrolment, gastrointestinal tract manifestations had occurred in more than half of the patients (55.7%). Also common were lung fibrosis (41.3%), pulmonary arterial hypertension (PAH) (15.0%) and heart manifestations (10.7%). Almost half of all patients (47.4%) were receiving treatment with bosentan or another ERA (endothelin receptor antagonist), with a similar proportion receiving calcium antagonists and approximately one third receiving prostanoids (see supplementary table S1, available online only).

Antibody distribution

Almost all, 95.7% (2085/2179), of patients tested were positive for antinuclear antibodies, 45.2% (854/1888) for anti-scleroderma-70 antibodies, 45.6% (775/1778) for ACA, 9.9% (86/867) for anti-RNA polymerase 3, and 49.9% (39/799) for anti-U1 ribonucleoprotein. Few patients had a combination of antibodies. The combination with the highest occurrence was anti-scleroderma-70 plus ACA, 2.5% (56/2439), followed by anti-scleroderma-70 plus anti-U1 ribonucleoprotein, 1.8% (43/2439), anti-scleroderma-70 plus anti-RNA polymerase 3, 1.5% (36/2439), ACA plus anti-U1 ribonucleoprotein, 1.4% (34/2439), ACA plus anti-RNA polymerase 3, 1.4% (34/2439) and anti-U1 ribonucleoprotein plus anti-U3 ribonucleoprotein, 1.3% (31/2439).

SSc disease characteristics by antibody status

Patients positive for ACA were predominantly classified as lcSSc (82.9%; table 1). From the patients positive for anti-scleroderma-70 antibodies, a high proportion were classified as dcSSc (66.6%) and a lower proportion were classified as lcSSc (29.4%). Lung fibrosis was most frequent in the anti-scleroderma-70 subset (62.2%) compared with other antibody subsets (22.3–41.9%). Gastrointestinal manifestations showed a similar high proportion in all antibody subgroups, except for patients who were anti-U3 ribonucleoprotein positive. The frequencies of PAH and kidney manifestations were generally similar across the antibody subsets, although the proportion among patients with anti-U3 ribonucleoprotein was slightly higher; heart manifestations were highest in patients with anti-scleroderma-70 and anti-U1 ribonucleoprotein and lowest in patients with ACA (table 2). The proportion of patients with previous digital ulcer complications and interventions was broadly similar in the anti-scleroderma-70 subgroup and the ACA subgroup; the most marked exception was for surgical amputation, which occurred almost twice as frequently in patients with ACA (14.6%) compared with anti-scleroderma-70-positive patients (7.9%) (table 3).
Table 2  Disease manifestations by antibody status

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>ANA (N=2085)</th>
<th>Anti-Scl-70 (N=854)</th>
<th>Anti-RNA Pol 3 (N=86)</th>
<th>ACA (N=775)</th>
<th>Anti-U1 RNP (N=120)</th>
<th>Anti-U3 RNP (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung fibrosis, n/N (%) (95% CI)</td>
<td>873/2085 (41.9) (39.7 to 44.0)</td>
<td>531/854 (62.2) (58.8 to 65.4)</td>
<td>36/86 (41.9) (31.3 to 53.0)</td>
<td>173/775 (22.3) (19.4 to 25.4)</td>
<td>50/120 (41.7) (32.7 to 51.0)</td>
<td>16/39 (41.0) (25.6 to 57.9)</td>
</tr>
<tr>
<td>PAH, n/N (%) (95% CI)</td>
<td>307/2085 (14.7) (13.2 to 16.3)</td>
<td>133/854 (15.6) (13.2 to 18.2)</td>
<td>12/86 (14.0) (7.4 to 23.1)</td>
<td>120/775 (15.5) (13.0 to 18.2)</td>
<td>10/120 (8.3) (4.1 to 14.8)</td>
<td>5/39 (12.8) (4.3 to 27.4)</td>
</tr>
<tr>
<td>Kidney manifestations, n/N (%) (95% CI)</td>
<td>105/2085 (5.0) (4.1 to 6.1)</td>
<td>43/854 (5.0) (3.7 to 6.7)</td>
<td>7/86 (8.1) (4.3 to 13.1)</td>
<td>26/775 (3.4) (2.2 to 4.9)</td>
<td>16/120 (13.3) (7.8 to 20.7)</td>
<td>2/39 (5.1) (1.8 to 9.7)</td>
</tr>
<tr>
<td>Gastrointestinal manifestations, n/N (%) (95% CI)</td>
<td>1192/2085 (57.2) (55.0 to 59.3)</td>
<td>486/854 (56.4) (56.4 to 63.9)</td>
<td>51/86 (59.3) (47.9 to 70.8)</td>
<td>440/775 (56.8) (53.2 to 60.3)</td>
<td>61/120 (50.8) (43.2 to 57.9)</td>
<td>15/39 (38.5) (23.4 to 55.4)</td>
</tr>
<tr>
<td>Heart manifestations, n/N (%) (95% CI)</td>
<td>220/2085 (10.6) (9.3 to 12.0)</td>
<td>105/854 (12.3) (10.2 to 14.7)</td>
<td>6/86 (7.0) (2.6 to 14.6)</td>
<td>47/775 (6.1) (4.5 to 8.0)</td>
<td>16/120 (13.3) (7.8 to 20.7)</td>
<td>3/39 (7.7) (1.6 to 20.9)</td>
</tr>
</tbody>
</table>

The denominator N varies according to the number of available observations.

*Antibody subsets are not mutually exclusive: one patient can have several antibodies and therefore contribute to several groups. ACA, anticiromere antibodies; ANA, antinuclear antibodies; anti-Scl-70, anti-scleroderma-70 antibodies; anti-RNA Pol 3, anti-RNA polymerase 3; anti-U1 RNP, anti-U1 ribonucleoprotein; anti-U3 RNP, anti-U3 ribonucleoprotein; PAH, pulmonary arterial hypertension.
was initiated following EMA approval of bosentan, and it is possible that patient entry into the registry was biased towards patients receiving bosentan. Therefore, there are limitations in the application of these data to the wider SSC population. Nevertheless, this study provides, and will continue to provide, valuable prospectively collected data from a large cohort of over 2000 SSC patients. The strengths include the prospective nature of data collection and the strong framework of research governance compared with that of previous studies. The multinational and multicentre nature of this registry offers the potential for comparison of different patient populations and healthcare systems.

CONCLUSION

This report provides the first analysis of data from the large, multinational DUO Registry confirming the high clinical burden of digital ulcers in patients with SSc across antibody subsets, with early occurrence and high frequency in patients with dcSSc. The feasibility and utility of the DUO Registry is confirmed by the findings of this study.

Contributors Registry design: CPD, TK, LG, BS, DR, MS, MZ, MMC; data acquisition: CPD, TK, LG, BS, DR, MS, MZ, MMC; statistical analysis: MS, DR. All authors were involved in the drafting and reviewing of the manuscript and approved the manuscript.

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Competing interests BS, DR, MS and MZ are employees of Actelion Pharmaceuticals Ltd, the manufacturers of bosentan. The non-Actelion employees who are authors of this manuscript have received consultancy fees or research grant funding from Actelion Pharmaceuticals Ltd.

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VALENCE; F SKOWRON
VALENCE; T ZENONE
VALENCIENNES; T QUEMENEUR, X KYNDT
VANDOUEVRVRE-LES-NANCY; D WAHL, S ZUILY, T MOLINE, V BRAVETTI

GR – GREECE
ALEXANDROUPOLIS; N GALANOPoulos
ATHENS; D VASILPOoulos
ATHENS; P VLACHYOANNOPoulos
HERAKLEIO/CRETA; I Kritikos
IOANNINA; N TSIfetaki
LARISSA; A KOUTROUMBAS
THESSALONIKI; A GARYFALLOs
THESSALONIKI; P ATHanasIASSIOu
THESSALONIKI; S ASLANIDIS
THESSALONIKI; S KAMALI
THESSALONIKI; T DIMITROULAS
THESSALONIKI; V GALANOPoulos
VOULA; A ELEZOGLou

IE – IRELAND
DUBLIN; A GRIER, M MURRAY, M O’ROURKE

IT – ITALY
ANCONA; A GABRIELLI
BARI; G LAPADULA
BARI; L SERAFINO, N TERRUZZI
BENEVENTO; S BELLISSIMO, S STISI
BOLOGNA; N MALAVOLTA
BRESCIA; P AIO
CAGLIARI; A VACCA
CATANIA; E BATTAGLIA
CATANIA; R FOTI
CATANZARO; S MAZZUCA
FERRARA; A BORTOLUZZI, F TROTta
FIRENZE; F GALLUCCIO
FOGGIA; A MARUCCI, F CANTATORE
FOGGIA; R BUCCI
GENOVA; F PUPPO
JESI; R DE ANGELI, W GRASSI
L’AQUILA; P CIPRIANI
LEGNANO; A MAZZONE, P FAGGIOLI
MILAN; A SEVERINO, R SCOrZA
MILAN; L BELLOLI, N UGHl
MILAN; M ANTIVALLE
MILAN; N DEL PAPA, W MAGLIONE
MILAN; S ZENI
MODENA; C FERRI, M COLACI
MORMANNO; G VARCASIa
NAPOlI; G CUOMO
PADUA; F COZZI
PALERMO; G TRIOLo
PASSIRANa DI RHo; S GATTI
PAVIA; CM MONTECUCCO
PISA; M DOVERI
POTENZA; A NIGRO, I OLIVIERI
REGGIO EMILIA; G BAJOCCHI
NL – THE NETHERLANDS

ALKMAAR; J D MOOLENBURGH
AMERSFOORT; AHM HEURKENS
AMSTERDAM; A VOSKUYL
AMSTERDAM; AE HAK, ESK STROES, J REMANS
AMSTERDAM; V GERDES
APELDOORN; JM VAN WOERKOM
ARNHEM; AJL DE LONG, HAH KAASJAGER, H VISser, M JANSSen
BRIDA; C VAN GULDENER, F VAN NEER, P VOS
DELT; AJ PETERS
DEN HAAG; H HULSMANS, K RONDAY, R GOEkoop
DEN HAAG; J EWALS, R VALENTuN
DEN HAAG; M DE BOIS
DEN HAAG; ML WESTEDT
DEVENTER; D SIEWERTSZ VAN REESEMA
EDE; E KNIFJU-DUTMER, JN STOLK
EINDHOVEN; H WILLEMs
EMmeloord; DG KUIPER-GEERTSMA, P BAUDAoIN
EMmEN; P FRETTER, R WESTRA
GOES; PBj SNoNNAVILLE
GRONINGEN; A SMIT, H BOOTSMA, L BROUWER, M BJL, N MOLDERS
HARDENBERG; C LEBRUN
HARDERWIJK; MJ VAN DER VEEN
HEERENVEEN; M NOORDZIJ
HEELEN; H HOUBEN, RMB LANDEWE, W VERCOUTERE
HILVERSUM; ZN JAHANGIER DE VEEN
HOOGVEEN; TR ZULSTRA
LEEuwArdEN; F UBELS, G BRuYN, P JANSEN
LEIDEN; A SCHUERWEgh, TWJ HUIZINGA
MAASTRICT; P PAASSEN, T HURKENS
NIeuwEgEN; M GEURTS
NIUMEGEN; F VAN DEN HooGEN
NIUMEGEN; M VONK
ROERMOND; PJC JACOBs
ROOSeNDaal; JHLM GRoENENDAEL, P SEYs
ROTTERDAM; D VAN ZEBEN, H VAN PAASSEN, J GRoENENDAEL
ROTTERDAM; KH HAN, M WLRVENs
ROTTERDAM; M VAN HAGEN, P VAN DAELe, R DOLHAIN
SCHIEDAM; AH GERARDS, P VAN DER LUBE
TILBURG; M DE KANTER, WH MUller
UtreCHT; E TON
VLISSINGEN; M VAN KRUGTEN
WINSCHOTEN; I VAN GAMEREn
WINTERSWIJK; P LANTING
WOERDEN; C DEN HENGST
NO – NORWAY
BERGEN; CG GIJSSDAL, SL HJERTAKER, TM MADLAND
KRYSTIANAND; A BENGOVOLD, H BITTER
OSLO; AM HOFFMANN-VOID, O MIDTVEDT
TROMSO; G BAKLAND, HK ASKAKSEN, M SEIP, S KALSTAD, W KOLDINGSNES
TRONDHEIM; B GRANDAENT, BY NORDVAG, EK STRAN, J SKOMSVOLL, M ANDERSEN, RS THOMSEN, T PEDERSEN, V BAKKEHEIM

PT – PORTUGAL
ALMADA; A CORDEIRO
AMADORA; J ALVES, S OLIVEIRA
LISBOA; P COelho
LISBO; C RESENDE, C PONTE
PORTO; J ALMEIDA, I SILVA
SANTAREM; C SANTOS, I CAMARA, J COSTA

SE – SWEDEN
FALUN; H HELLSTROM
Helsingborg; A MOHAMMAD
KARLKRONA; I LIND, K LIND, T BRACIN
KARLSTAD; E LILJEEQUIST, T VINGREN
KRISTIANDSTAD; A OSTENSON
LINKONP; E HERMANSSON
OSKARSTROM; C THORSSON, M SODERLIN
STOCKHOLM; A NORDIN, E WALDHEIM, K VENEMYR, K ALBERTSSON, ML KARLSSON, Y RYDVALD
VASTERS; M RIZK

SI – SLOVENIA
LIUBLJANA; AS DOLNICAR

SK – SLOVAKIA
PIESTANY; J LUKAC

UK – UNITED KINGDOM
BATH; J JAMES, N MCHugh, S COLE, S BROWN
BELFAST; A HAMILTON
BIRMINGHAM; A FAZAL
CAMBRIDGE; F HALL, K MURPHY, S SKINGLE
FIFE; H HARRIS
GLASGOW; F MADHOK, R HAMPSH
HULL; E BAGULEY, O OGUNBAMI
LIVERPOOL; J LAMB, M ANDERSON, R MOOTS
LONDON; B WHITE-ALAO, C MORRISON, J DOBSON, P GORDON, R SALERNO
LONDON; C DENTON, L PARKER, R OCHIELI, R VINCENT, Z ZIMBA, T NGCOZANA, Y XU
LONDON; D D’CRUZ, LM CHOONG
MANCHESTER; A HERRICK, E WRAGG, J MANNING, T MOORE
ROMFORD; C KELSEY, K CHAKRAVARTY
SOUTHPORT; H SKYES
WORCESTER; P ATHIVEER
**Supplementary table**

**Table S1: Ongoing medications/therapies at enrolment**

<table>
<thead>
<tr>
<th>Medications/therapies (use for any reason)</th>
<th>Number of patients, n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-opioid analgesics and NSAIDs</td>
<td>714 (29.3)</td>
</tr>
<tr>
<td>Opioids</td>
<td>238 (9.8)</td>
</tr>
<tr>
<td>Corticoids</td>
<td>792 (32.5)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>438 (18.0)</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>717 (29.4)</td>
</tr>
<tr>
<td>Systemic antibiotics</td>
<td>344 (14.1)</td>
</tr>
<tr>
<td>ERA**</td>
<td>1157 (47.4)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1058 (43.4)</td>
</tr>
<tr>
<td>Prostacyclins</td>
<td>828 (33.9)</td>
</tr>
<tr>
<td>Phosphodiesterase-5 inhibitors</td>
<td>124 (5.1)</td>
</tr>
<tr>
<td>Other medications</td>
<td>1616 (66.3)</td>
</tr>
<tr>
<td>Topical DU treatments</td>
<td>520 (21.3)</td>
</tr>
</tbody>
</table>

*Denominator = all patients = 2439; **ERA= bosentan or other ERA; DU, digital ulcer; ERA, endothelin receptor antagonist