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# A Randomized Phase II Crossover Study of Imatinib or Rituximab for Cutaneous Sclerosis after Hematopoietic Cell Transplantation

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## Abstract

**Purpose:** Cutaneous sclerosis occurs in 20% of patients with chronic graft-versus-host disease (GVHD) and can compromise mobility and quality of life.

**Experimental design:** We conducted a prospective, multicenter, randomized, two-arm phase II crossover trial of imatinib (200 mg daily) or rituximab (375 mg/m$^2$ i.v. weekly × 4 doses, repeatable after 3 months) for treatment of cutaneous sclerosis diagnosed within 18 months (NCT01309997). The primary endpoint was significant clinical response (SCR) at 6 months, defined as quantitative improvement in skin sclerosis or joint range of motion. Treatment success was defined as SCR at 6 months without crossover, recurrent malignancy or death. Secondary endpoints included changes of B-cell profiles in blood (BAFF levels and cellular subsets), patient-reported outcomes, and histopathology between responders and nonresponders with each therapy.

**Results:** SCR was observed in 9 of 35 [26%; 95% confidence interval (CI); 13%–43%] participants randomized to imatinib and 10 of 37 (27%; 95% CI, 14%–44%) randomized to rituximab. Six (17%; 95% CI, 7%–34%) patients in the imatinib arm and 5 (14%; 95% CI, 5%–29%) in the rituximab arm had treatment success. Higher percentages of activated B cells ($CD27^+$) were seen at enrollment in rituximab-treated patients who had treatment success ($P = 0.01$), but not in imatinib-treated patients.

**Conclusions:** These results support the need for more effective therapies for cutaneous sclerosis and suggest that activated B cells define a subgroup of patients with cutaneous sclerosis who are more likely to respond to rituximab. *Clin Cancer Res; 22(2); 319–27.* ©*2015 AACR.*

## Introduction

Cutaneous sclerosis associated with chronic graft-versus-host disease (GVHD) can severely affect mobility and quality of life and is a major cause of disability and morbidity after allogeneic hematopoietic cell transplantation (HCT). A recent multicenter prospective study of 909 HCT recipients reported a 10% 2-year cumulative incidence of cutaneous sclerosis after HCT (1). The 3-year cumulative incidence of cutaneous sclerosis was 20% among the largest reported retrospective study of 977 patients with chronic GVHD (2). Cutaneous sclerosis is often refractory to immunosuppressive therapy. Advanced cutaneous sclerosis causes joint contractures, chronic skin ulcers, pulmonary insufficiency due to thoracic encasement, and other disabilities. Risk factors for cutaneous sclerosis among patients with chronic GVHD and the potential impact of cutaneous sclerosis on transplant outcomes have been reported (2–4). Use of a mobilized peripheral blood graft and total body irradiation in the transplant conditioning regimen were associated with an increased risk of cutaneous sclerosis (2, 3). No increased risk of overall mortality, nonrelapse mortality, or recurrent malignancy has been found in patients with cutaneous sclerosis compared with chronic GVHD patients without cutaneous sclerosis, but the development of cutaneous sclerosis was associated with longer time to withdrawal of immunosuppressive treatment for chronic GVHD (2).

The pathogenesis of cutaneous sclerosis is not understood. Although cutaneous sclerosis has some clinical and histopathologic similarities with systemic sclerosis (SSc), some differences are noted. For instance, cutaneous sclerosis begins in the upper

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**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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## Translational Relevance

Chronic graft-versus-host disease (GVHD) is a syndrome in which the contributions of inflammation, innate and adaptive cell-mediated immunity, humoral immunity, abnormal immune regulation, and fibrosis vary from one patient to the next. Cutaneous sclerosis is a form of chronic GVHD where fibrosis of skin and fascia predominate. In this multicenter, randomized, two-arm, phase II crossover trial of imatinib or rituximab for cutaneous sclerosis, there was a statistically significant ($P = 0.01$) higher percentage of activated B cells ($CD27^+$) before treatment in the rituximab patients who had treatment success compared with those who did not, suggesting that activated B cells may be a good marker for patients with cutaneous sclerosis who will respond to rituximab. This relationship was not seen in imatinib-treated patients. Although the number of analyzed cases is small, this finding adds further evidence for the role of B cells in the pathogenesis of sclerosis in chronic GVHD.

dermal layers and then extends more deeply, whereas SSc begins in the deeper skin layer and then extends toward the surface (5). Intimal hyperplasia is seen in both chronic GVHD and SSc, but capillary rarefaction and loss of endothelial-specific markers were not seen in chronic GVHD as they are in SSc (6). Still, the molecular stimuli for fibrosis could be similar in the two diseases.

Stimulatory antibodies against the platelet-derived growth factor receptor (PDGFR) have been identified in patients with SSc and cutaneous sclerosis in chronic GVHD (7, 8). This observation has served as the rationale for testing imatinib, an inhibitor of signaling through PDGFR, as a treatment for cutaneous sclerosis. Imatinib has been reported to have clinical activity against sclerotic chronic GVHD (9–11). Another hypothesis is that dysregulated donor B-cell responses result in the sclerotic phenotype. Accumulating data suggest high levels of B-cell activating factor (BAFF) after allogeneic HCT promote the survival of allo- and autoreactive B cells and cause persistent activation of B-cell signaling pathways in chronic GVHD (12, 13). In patient B cells and in murine models, inhibition of B-cell signaling can prevent or reverse tissue injury caused by chronic GVHD (14, 15). Rituximab has broad immunoregulatory effects and has shown promising activity in patients with chronic GVHD as a B-cell–depleting therapy (16–19).

In this prospective clinical trial targeting cutaneous sclerosis associated with chronic GVHD, we tested whether imatinib or rituximab could improve the clinical manifestations of cutaneous sclerosis.

## Materials and Methods

### Participants

Participants were enrolled at 11 institutions within the Chronic GVHD Consortium (NCT01309997). The protocol was IRB-approved at each site. Informed consent was obtained in accordance with the Declaration of Helsinki. Participants were enrolled in the study between March 2011 and June 2014, and the data were analyzed as of January 31, 2015.

Eligible patients were children or adults diagnosed within the past 18 months with cutaneous sclerosis after allogeneic HCT, with no medication added for the treatment of GVHD within the past 4 weeks. Participants were receiving corticosteroids at a dose greater than required for treatment of adrenal insufficiency unless the physician documented why steroids were contraindicated, but documentation of steroid dependence or refractoriness was not required. Cutaneous sclerosis was defined as sclerotic skin, morphea-like involvement, myofascial involvement, or joint contractures [a Vienna Skin Score (VSS) $\geq$2 in any area (ref. 20), or Photographic Range of Motion (P-ROM) score of 5 or less at the shoulders, elbows, or wrists, or a score of 3 or less at the ankles; ref. 21]. Exclusion criteria included treatment with imatinib within the previous 6 months for any indication, treatment with any monoclonal B-cell antibody therapy (e.g., rituximab, ofatumumab) within the previous 12 months for any indication, and concomitant treatment with extracorporeal photopheresis (ECP). Concomitant treatment with sirolimus was also not permitted initially because of potential interactions with imatinib, but this study exclusion was removed later.

### Study design

The study was designed as a prospective, multicenter, open-label, randomized phase II trial of imatinib (200 mg daily by mouth, provided by Novartis) or rituximab (375 mg/m$^2$ intravenously weekly $\times$ 4 doses, repeatable after 3 months, provided by Genentech) for the treatment of cutaneous sclerosis. Randomization was stratified by center and baseline steroid dose (<30 mg/d vs. >30 mg/d).

The primary objective of the trial was to determine the clinical response rate of cutaneous sclerosis after 6 months of initial therapy with either imatinib or rituximab. The primary endpoint was the significant clinical response (SCR) rate at 6 months, defined as a 2 or more point improvement on the VSS without worsening elsewhere or at least a 1-point improvement in the 4-level P-ROM scale or a 2-point improvement in the 7-level scale without worsening elsewhere. Crossover to the other study arm was allowed at 6 months if cutaneous sclerosis did not improve, or earlier for cutaneous sclerosis progression or drug intolerance. Cutaneous sclerosis progression was defined as a 2-point or more worsening on the VSS or a 1-point worsening in the 4-level P-ROM scale or a 2-point worsening in the 7-level scale, although crossover was also allowed for clinical worsening not fulfilling these criteria. Treatment success was defined as SCR at 6 months without crossover to the other arm, recurrent malignancy or death.

Secondary endpoints of the study included in this report are the following: (i) the cumulative incidence of treatment failure defined as failure to achieve an SCR at the 6 month assessment, crossover to the other arm, or stopping initial treatment due to toxicity, (ii) the proportion of patients able to decrease their daily corticosteroid dose to <50% of their enrollment dose, (iii) the proportion of patients with any body surface area (BSA) percentage decline in sclerosis without BSA increase in the percentage of higher grades of sclerosis elsewhere according to the VSS, (iv) correlation of changes in patient-reported outcomes with response, and (v) correlation of changes in skin biopsy histology and B-cell profiles in blood (cytokine and cellular subsets) between responders (SCR) and nonresponders with each therapeutic agent.

Clinician assessments using the VSS (Supplementary Fig. S1), P-ROM (Supplementary Fig. S2), and NIH chronic GVHD consensus conference scoring system (22) and patient self-reported outcomes (SHAQ; refs. 23, 24), FACT-BMT, Short Form 36 (SF36; ref. 25), Lee symptom scale (26), and health activity profile (HAP;

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ref. 27) were performed at study enrollment and months 3, 6, 9, 12, and 18. Clinicians were also asked to qualitatively rate patients' response in skin and joint chronic GVHD at 6 months on an 8-point scale of resolved/very much better/moderately better (better), a little better/stable/a little worse (stable), and moderately worse/very much worse (worse).

### Laboratory correlates

Whole blood samples were drawn into ethylenediaminetetraacetic acid (EDTA) and heparin-containing tubes at study enrollment and at 6 months after initial randomization to each treatment arm or at time of cross over, whichever occurred first. Plasma was separated from whole blood cells by centrifugation at 600 g and stored at −80°C until first thaw and batch testing. Soluble BAFF was measured using a commercially available ELISA as previous described (28). Fresh blood in EDTA was shipped to the Sarantopoulos laboratory from the study sites and analyzed within 36 hours. Whole blood was processed for flow cytometry as previously described using antibodies directed at CD3, CD19, and CD27. Lymphocytes were gated by size using forward and side scatter criteria. A minimum of 50,000 lymphocytes were collected for all samples to ensure adequate subset analysis. Cells were analyzed using BD Canto and FlowJo 10 analysis software.

### Histopathology correlates

Two 3-mm skin biopsies were obtained from participants at a leading edge of sclerosis at study enrollment and at 6 months after initial randomization to each treatment arm or at time of cross over, whichever occurred first. The sites were the same unless there was a clinical contraindication. All skin biopsy slides were stained with hematoxylin and eosin (H&E). Two pathologists (T.S. Hyun and H.M. Shulman) concurrently reviewed the slides with a double-headed microscope blinded to all clinical details, including treatment for GVHD, to reach a consensus about the sclerosis grade from 0 to 5 according to a previously published scale used to assess regression of sclerosis after autologous HCT for systemic sclerosis (29).

### Statistical design and analysis

When the study was designed, no preliminary data were available to estimate the response rate of cutaneous sclerosis associated with chronic GVHD using the NIH Consensus Diagnosis Criteria (22). Thus, a target enrollment of 74 patients was proposed so that 70 patients could be evaluated for the primary endpoint (35 per arm). With 35 patients, the proportion of SCR could be estimated within approximately 15% of the actual response rate at 6 months (primary endpoint) after treatment with each agent, based on a 95% confidence interval. Improvement would not be expected in the absence of effective therapy. All participants who received treatment with imatinib for at least 1 week or at least one dose of rituximab were evaluable for the primary endpoint.

Overall responses of cutaneous sclerosis were assessed by the medical provider using semiquantitative measures (see Supplementary Figs. S1 and S2) and by patients using the SHAQ, a validated instrument for patients with SSc (23, 24). The response endpoint was calculated at 6 months by comparison of baseline and 6-month assessments. True discordance in response (improvement in one measure while worsening in the other) was considered progression. Cumulative incidences of treatment failure were estimated by standard methods.

Baseline and change scores in patient-reported outcomes, laboratory markers, and histopathologic grades in skin biopsy samples were compared between treatment arms and between subgroups achieving treatment success versus those that did not have treatment success in each treatment arm.

## Results

Of 72 patients enrolled in this study between March 2011 and June 2014, 35 were randomized to imatinib and 37 to rituximab. The patient flow diagram is shown in Fig. 1. Table 1 displays study participant characteristics. The median age was 56 years (range, 19–77), 56% were male, and all had organs other than skin involved with chronic GVHD at study enrollment. The median time from chronic GVHD onset to study enrollment was 1 year (range, 0–3.8 years). The median follow-up among 54 surviving participants is 19.5 months (range, 5.3–47.5 months) from study enrollment.

### Safety and adverse events/infections

Adverse events observed for treatment with imatinib or rituximab were similar to those reported for treatment of patients with chronic GVHD. The grade 3 to 5 toxicities reported to be possibly, probably, or definitely attributed to imatinib or rituximab are shown in the Supplementary Table. Most events were infectious in nature, primarily respiratory or skin infections, with 2 deaths each in the imatinib and rituximab arms potentially attributable to the study drug. All 4 deaths were due to respiratory complications. In the imatinib arm, the deaths were caused by aspergillus pneumonia and parainfluenza pneumonia. In the rituximab arm, the deaths were caused by Pneumocystis jirovecii pneumonia in a patient who was receiving Bactrim prophylaxis, and aspergillus pneumonia. One patient in the rituximab arm had a grade 3 infusional toxicity that resolved with additional medication. As expected, grade 3 to 4 neutropenia occurred more frequently in the rituximab arm.

### Clinical responses after initial treatment

Disposition of study participants is shown in Fig. 1. Of 72 participants, 61 were fully evaluable for the primary endpoint after initial randomization (30 in the imatinib arm and 31 in rituximab treatment arm) based on enrollment and 6-month clinician-reported data. Eleven patients did not have 6-month data available for the reasons detailed in Fig. 1.

Clinical responses and other outcomes after initial randomization to imatinib or rituximab are summarized in Table 2. SCR was observed in 9/35 (26%, 95% CI 13%–43%) participants randomized to imatinib and 10/37 (27%, 95% CI 14%–44%) randomized to rituximab. Among patients with SCR, 3 in the imatinib arm and 5 in the rituximab arm crossed over due to clinician-perceived lack of adequate response despite SCR. In 7 of these cases, improvement in one or more areas was recognized, but overall the response of the sclerosis was not deemed sufficient to continue on initial treatment. In one case, the patient was thought to have an SCR at 6 months but crossed over shortly thereafter when sclerosis worsened.

Six (17%; 95% CI, 7%–34%) patients in the imatinib arm and 5 (14%; 95% CI, 5%–29%) in the rituximab arm had treatment success defined as attaining an SCR without crossover, relapse or death at 6 months. Of the 35 participants randomized to imatinib, 7 completed at least 6 months of treatment with imatinib, did not cross over to rituximab and remain alive; of these, two patients are

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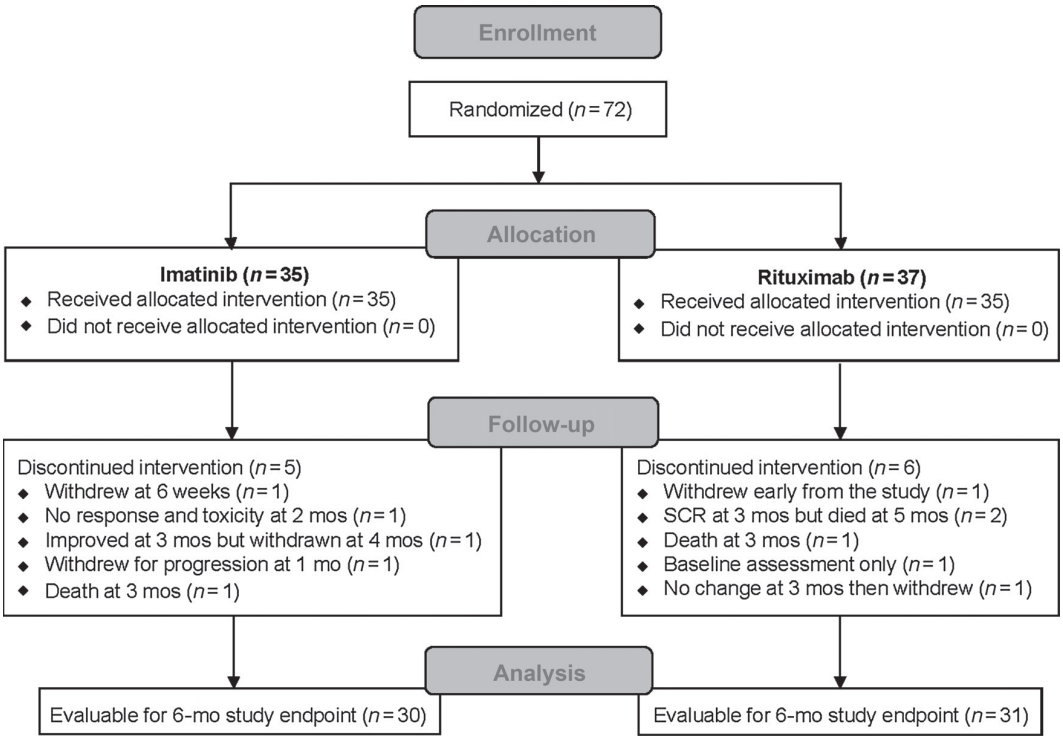


**Figure 1.**
Disposition of trial participants.

continuing treatment with imatinib. Of the 37 participants randomized to rituximab, 10 completed one or two courses of treatment with rituximab, never crossed over to imatinib, and remain alive.

The cumulative incidence of treatment failure defined as less than an SCR at the 6-month assessment or discontinuation of randomized treatment due to chronic GVHD progression or treatment intolerance within 6 months after initial randomization was 65% (95% CI, 51%–83%) for patients in the imatinib arm and 58% (95% CI, 44%–77%) for the rituximab arm (Figure 2). Eleven patients (5 imatinib and 6 rituximab) could not be confirmed as either treatment success or treatment failure due to either early withdrawal for reasons other than cutaneous sclerosis progression or treatment intolerance, or lack of 6-month clinician-reported endpoint data.

The proportion of patients at the 6-month visit able to decrease daily corticosteroids dose to 50% or less than the baseline dose was 26% (7/27) and 29% (9/32) among patients who could be evaluated in the imatinib and rituximab arms, respectively. The proportion of all patients at the 6-month visit with any percentage BSA decline (improvement) in total movable or nonmovable sclerosis without increase in the percentage of nonmovable sclerosis was 47% (14/30) in the imatinib arm and 29% (9/31) in the rituximab arm. The proportion of patients at 6-months with increase (improvement) in the P-ROM in any joint without decreased (worsening) in other joints was 13% (4/30 evaluable patients) with imatinib and was 32% (10/31 evaluable patients) with rituximab.

Clinicians' qualitative assessments of skin response at 6 months was 26% better, 52% stable, 11% worse, and 11% missing in the imatinib arm and 16% better, 54% stable, 16% worse, and 14% missing in the rituximab arm. For joints, clinicians reported 17% better, 54% stable, 6% worse, and 23% missing in the imatinib arm and 3% better, 73% stable, 3% worse and 21% missing in the rituximab arm.

### Clinical responses after crossover

Among 18 patients who crossed over to the rituximab arm, 5 experienced an SCR by 6 months after crossover, 2 have not yet been followed for 6 months, and 11 others either withdrew without response ($n = 2$), died ($n = 1$), or did not have an SCR ($n = 8$), for a treatment success rate of 5 of 16 (31%) among those with at least 6 months of follow-up after crossover. Among 17 patients who are alive and crossed over to the rituximab treatment arm, 10 patients have not required new treatment for cutaneous sclerosis at the time of this analysis. Among 23 patients who crossed over to the imatinib arm, 4 experienced an SCR by 6 months after crossover, 2 have not been followed for 6 months, and 15 did not (4 withdrew without response, 2 withdrew due to toxicity, 3 died, 6 did not have an SCR), for a treatment success rate of 4/21 (19%) among those with at least 6 months of follow up after crossover. Among 14 patients who are alive and crossed over to the imatinib arm, 8 have not required new treatment for cutaneous sclerosis and 2 patients continue this treatment at the time of this analysis.

### Patient self-reported outcomes

We evaluated whether sclerosis-related symptoms measured by the SHAQ standard disability index correlated with severity of

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**Table 1.** Participant characteristics according to randomization

| Characteristic | All patients ($n = 72$) | Initial treatment | |
|---|---|---|---|
| | | Imatinib ($n = 35$) | Rituximab ($n = 37$) |
| Patient age, median (range) | 56 (19–77) | 56 (19–72) | 56 (21–78) |
| Male patient, *n* (%) | 40 (56) | 18 (51) | 22 (59) |
| Female donor to male recipient, *n* (%) | 15 (21) | 7 (20) | 8 (22) |
| Advanced (high-risk) disease at transplantation, *n* (%) | 16 (22) | 9(26) | 7(19) |
| Conditioning regimen, *n* (%) | | | |
| Myeloablative | 41 (57) | 26 (74) | 15 (41) |
| Reduced intensity or non-myeloablative | 31 (43) | 9(26) | 22 (59) |
| Graft source, *n* (%) | | | |
| Mobilized blood cells | 67 (94) | 32 (94) | 35 (95) |
| Bone marrow | 3 (4) | 1 (3) | 2 (5) |
| Cord blood | 1 (1) | 1 (3) | 0 (0) |
| Donor type, *n* (%) | | | |
| HLA fully matched related | 24 (33) | 15 (43) | 9 (24) |
| HLA fully matched unrelated | 36 (50) | 12 (34) | 24 (65) |
| HLA mismatched related or unrelated | 12 (17) | 8 (23) | 4 (11) |
| Time from transplantation to chronic GVHD, median (range), months | 11 (0.4–82) | 11 (0.7–82) | 11 (0.4–44) |
| Time from transplant to study enrollment, median (range), months | 29 (8–87) | 31 (8–87) | 27 (14–61) |
| Presence of GVHD sites involved at enrollment, *n* (%) | | | |
| Skin | 70 (99) | 34 (100) | 36 (97) |
| Eyes | 47 (65) | 21 (60) | 26 (70) |
| Mouth | 39 (54) | 20 (57) | 19 (51) |
| Liver | 23 (44) | 11 (46) | 12 (43) |
| Gastrointestinal tract | 19 (26) | 10 (29) | 9 (24) |
| Lung | 26 (37) | 11 (31) | 15 (42) |
| Joint or fascia | 65 (90) | 31 (89) | 34 (92) |
| Genital tract | 11 (16) | 7 (20) | 4 (11) |
| NIH global score at study enrollment, *n* (%) | | | |
| Moderate | 19 (26) | 11 (31) | 8 (22) |
| Severe | 53 (74) | 24 (69) | 29 (78) |
| Subcategory of chronic GVHD at enrollment, *n* (%) | | | |
| Classic | 14 (19) | 8 (23) | 6 (16) |
| Overlap | 58 (81) | 27 (77) | 31 (84) |
| Karnofsky score <80% at study enrollment, *n* (%) | 30 (44) | 14 (42) | 16 (46) |
| Prior grades II–IV acute GVHD, *n* (%) | 31 (46) | 17 (55) | 14 (39) |
| Prednisone dose at study enrollment, *n* (%) | | | |
| None | 8 (12) | 6 (19) | 2 (6) |
| <0.5 mg/kg daily | 43 (64) | 18 (58) | 25 (69) |
| ≥0.5 mg/kg daily | 16 (24) | 7 (23) | 9 (25) |
| Other treatment of chronic GVHD at enrollment, *n* (%) | | | |
| Calcineurin inhibitor | 36 (50) | 19 (54) | 17 (46) |
| Sirolimus | 7 (10) | 2 (6) | 5 (14) |
| Mycophenolate mofetil | 6 (8) | 4 (11) | 2 (5) |
| Others | 29 (40) | 14 (40) | 15 (41) |
| Number of agents plus initial randomized agent, *n* (%) | | | |
| 2 | 65 (90) | 30 (86) | 35 (95) |
| ≥3 | 7 (10) | 5 (14) | 2 (5) |
| Time from onset of sclerosis to enrollment, median months (interquartile range) | 1.8 (0.5–5.7) | 1.6 (0.2–6.1) | 2.3 (0.6–4.1) |

cutaneous sclerosis by clinical findings and response to study treatment. The SHAQ score did not correlate with the percentage of total body surface with movable or nonmovable sclerosis using the VSS, but did correlate with total P-ROM (Spearman correlation coefficient $-0.41$, $P = 0.001$). Compared with enrollment, 11 evaluable patients had their SHAQ standard disability index decrease by at least 0.2 UI, which is considered a clinically meaningful difference, but improvement in the SHAQ was not correlated with treatment success in either arm.

Changes in other patient-reported outcomes were correlated with treatment arms and treatment success. The only significant difference at $P < 0.01$ was a median 10-point decrease (range $-55$ to $+25$) to $P = 0.001$ for the Lee skin symptom scale for the imatinib arm. There were no differences in the other Lee subscale scores, the SF-36, FACT-BMT, or HAP for the imatinib arm, and no statistically significant changes for any of these scales in the rituximab arm. The correlation of changes in patient-reported outcomes and treatment success were evaluated for 28 patients in the imatinib arm (6 treatment successes) and 23 in the rituximab

**Table 2.** Summary of overall clinical results

| Outcome | Initial randomization | |
|---|---|---|
| | Imatinib $n = 35$ | Rituximab $n = 37$ |
| Significant clinical response (SCR), *n* (%) | 9 (26) | 10 (27) |
| Treatment success: SCR without crossover, relapse or death at 6 months | 6 (17) | 5 (14) |
| Treatment failure at 6 months, *n* | 29 | 32 |
| No SCR[a], *n* | 21 | 21 |
| Crossover to other arm[a], *n* | 18 | 23 |
| Not evaluable[b], *n* | 5 | 6 |

[a]Totals >100% because reasons are not mutually exclusive.
[b]See disposition of study participants shown in Fig. 1.

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