

## PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/172357>

Please be advised that this information was generated on 2020-11-23 and may be subject to change.

## CLINICAL REPORT

# Drug Survival and Predictors of Drug Survival for Methotrexate Treatment in a Retrospective Cohort of Adult Patients with Localized Scleroderma

Jorre S. MERTENS<sup>1,4</sup>, Juul M. VAN DEN REEK<sup>1</sup>, Wietske KIEVIT<sup>2</sup>, Peter C. M. VAN DE KERKHOF<sup>1</sup>, Rogier M. THURLINGS<sup>3</sup>, Tim R. D. RADSTAKE<sup>4</sup>, Marieke M. B. SEYGER<sup>1</sup> and Elke M. G. J. DE JONG<sup>1</sup>

Departments of <sup>1</sup>Dermatology, <sup>2</sup>Epidemiology, Health Evidence, <sup>3</sup>Rheumatology, Radboud University Medical Center, Nijmegen, and <sup>4</sup>Department of Rheumatology and Clinical Immunology and Laboratory of Translational Immunology, University Medical Center Utrecht, Utrecht, The Netherlands

**Data regarding the efficacy and safety of methotrexate (MTX) in adults with localized scleroderma (LoS) is scarce. This study gathered data from a retrospective cohort of adult patients with LoS ( $n=107$ ), treated with MTX (1993–2015). MTX drug survival and predictors thereof were analysed. After 1 and 2 years, 26% and 63% of patients stopped MTX due to disease remission, respectively. Patients with younger age at MTX initiation (hazard ratio (HR) 1.159 (95% confidence interval (CI) 1.052–1.277)) and those with no other autoimmune diseases (HR 3.268 (95% CI 1.334–8.009)) more often stopped MTX due to disease remission. In addition, 24% of patients stopped MTX due to treatment failure within one year. Patients with circumscribed superficial LoS (HR 0.221 (95% CI 0.081–0.601)) experienced treatment failure less often than those with other LoS subtypes. Finally, adding folic acid (HR 0.184 (95% CI 0.079–0.425)) and reducing treatment delay (HR 1.056 (95% CI 1.004–1.112)) could be the most important factors in minimizing MTX treatment failure in LoS in clinical practice. *Key words: localized scleroderma; morphea; methotrexate, treatment.***

Accepted Mar 10, 2016; Epub ahead of print Mar 17, 2016

Acta Derm Venereol 2016; 96: 943–947.

Jorre S. Mertens, Department of Dermatology 370, Radboud University Medical Centre, René Descartesdreef 1, NL-6525 GL Nijmegen, The Netherlands. E-mail: Jorre.Mertens@radboudumc.nl

Localized scleroderma (LoS), also known as morphea, encompasses a spectrum of rare diseases causing fibrosis of the skin and underlying tissues, such as fat, fascia and muscle (1). Local sclerosis can cause extensive morbidity, such as joint contractures, limb length discrepancies and muscle weakness, due to active myositis or muscle atrophy (2). This extensive morbidity in combination with the disease, in general, has a significant impact on quality of life and requires adequate treatment (3, 4).

Methotrexate (MTX), with or without concomitant systemic corticosteroids, is recommended as the primary treatment option in patients with moderate to

severe or treatment refractory disease (5–7). However, data regarding the efficacy and safety of MTX in adult patients with LoS is scarce; to date only 3 studies have reported original data regarding MTX treatment in adults with LoS (8–10). As MTX is the most prescribed systemic treatment for LoS, there is an urgent need for more evidence regarding treatment strategies.

The main objective of this study was to describe drug survival for MTX treatment in a large long-term daily practice cohort of patients with LoS. Drug survival analyses allow evaluation of treatment duration with a particular drug with regards to different outcomes of interest. Drug survival is a comprehensive outcome covering effectiveness, safety, and patients' and doctors' preferences (11). We investigated the drug survival split for disease remission and treatment failure. In addition, by identifying predictors of drug survival for MTX we aimed to improve treatment strategies.

## METHODS

### *Patients and data collection*

A retrospective chart review of adult patients with LoS treated with MTX was performed. All patients were evaluated at the combined dermatology and rheumatology outpatient clinic at Radboud University Medical Center (Nijmegen, The Netherlands) between August 1993 and July 2015. The first treatment episode with MTX was included for analysis. The following information was collected: age at treatment initiation, route of administration, dosage alterations, overall treatment duration and prescription of folic acid or concomitant systemic corticosteroids.

### *Reasons for treatment discontinuation*

The first reason for treatment discontinuation was disease remission, which was present if the treating physician reported a satisfactory result at treatment cessation. The second reason for treatment discontinuation was treatment failure, which, for subanalyses, was split into side-effects and treatment ineffectiveness. Ineffectiveness was present if the treating physician reported an unsatisfactory treatment result. In addition, patients could be categorized as having a mixture of reasons for stopping treatment (i.e. side-effects and ineffectiveness). Finally, patients could be categorized as having another reason for stopping treatment (i.e. patient's wish or elective surgery).

### Predictors of drug survival

In order to understand the selection procedure for possible predictors, Cox-regression analyses allowed us to investigate associations between baseline variables and an outcome of interest. Treatment-specific variables in this context are, however, confounded by indication and should not be analysed using this method. Therefore, we selected the following baseline characteristics as candidate predictors: sex, age at disease onset, calendar year at MTX initiation, time between disease onset and MTX initiation (treatment initiation delay), disease subtype as reported by Laxer & Zulian (12), prescription of folic acid at MTX initiation, presence of anti-nuclear antibodies (ANAs), and presence of concomitant autoimmune diseases. To investigate whether drug survival of MTX was influenced by treatment behaviour, calendar year at MTX initiation was added as a possible predictor.

### Statistical analysis

Descriptive statistics, including median and range for continuous variables and percentages for categorical data, were used to explore baseline and patient characteristics. Drug survival analyses were performed using Kaplan–Meier curves for MTX drug survival related to treatment failure and split for side-effects and treatment ineffectiveness. For the purpose of visualization drug survival related to disease remission was displayed as one minus survival curves. Treatment episodes were censored for a particular survival analysis when patients were still being treated at data lock, were lost to follow-up, or discontinued MTX for a reason other than the reason of interest. An MTX treatment episode was considered discontinued when MTX was interrupted for more than 21 days.

Potential predictors were selected using a univariate Cox regression model separately for each different discontinuation reason. Determinants with a  $p$ -value  $\leq 0.2$  were imported in a multivariate Cox regression model with backward selection. As a rule of thumb, multivariate Cox regression analyses allow us to import one predictor of interest per 10 events for the discontinuation reason of interest (11). If the number of possible predictors identified by univariate analyses exceeded the number of predictors allowed in a multivariate model, we selected the predictors with the strongest association based on  $p$ -values. Predictors are displayed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Statistical analyses were performed using SPSS Statistics v.22 (IBM, Armonk, NY, USA).

## RESULTS

### Baseline characteristics

In total, 113 patients with LoS using MTX were identified. A total of 107 (94.7%) patients were included for drug survival analysis. The remaining 6 patients were excluded due to incomplete data regarding MTX treatment. Baseline characteristics of the 107 patients, 77 females (72.0%) and 30 males (28.0%) (ratio 2.6:1), are shown in Table I. The median age at disease onset was 46 years (range 2–77 years). Subtype distribution is shown in Table I.

### Treatment characteristics

Details of the MTX treatment are summarized in Table II. The median age at MTX initiation was 49 years (range 18–78 years) and the median time between di-

Table I. Demographics and subtype distribution in 107 subjects with localized scleroderma (LoS) treated with methotrexate (MTX)

Characteristics	Adult <i>n</i> = 107
Female:male, <i>n</i> (ratio)	77:30 (2.6:1.0)
MTX initiation, age, years, median (range)	49 (18–78)
Onset of LoS, age, years, median (range)	46 (2–77)
Subtypes, <i>n</i> (%)	
Circumscribed	
Superficial	27 (25.2)
Deep	12 (11.2)
Linear	
Trunk/limbs	18 (16.8)
Head	1 (0.9)
Generalized	33 (30.8)
Mixed	16 (15.0)

sease onset and MTX initiation was 18 months (range 3–429 months). The median MTX treatment duration was 49 weeks (range 4–261 weeks). In general, patients received MTX 15 mg/week (range 5.0–26.9 mg/week) during the treatment episode. The median maximum dose was 15 mg (range 5.0–30 mg). Finally, 37 (34.6%) patients were concomitantly treated with systemic corticosteroids and 78 (72.9%) patients received folic acid.

### Reasons for methotrexate discontinuation

In 44 (41.1%) of 107 patients, disease remission was the sole reason to stop MTX. Side-effects or treatment ineffectiveness, with no other reason, was a reason to discontinue MTX treatment in 12 (11.2%) and 14 (13.1%) patients, respectively. In total, 8 patients (7.5%) had a combination of stopping reasons: 4 (3.7%) had a combination of disease remission and side-effects, and 4 (3.7%) experienced treatment ineffectiveness and side-effects. Side-effects severe enough to lead to MTX discontinuation were gastro-intestinal symptoms ( $n = 7$ , 6.5%), laboratory abnormalities ( $n = 7$ , 6.5%), consisting of 5 patients (4.7%) with signs of hepatotoxicity and 2 (1.9%) of haematotoxicity,

Table II. Treatment characteristics in 107 subjects with localized scleroderma treated with methotrexate (MTX). Delay in MTX initiation was measured as the time between disease onset and MTX initiation

Characteristics	Adult <i>n</i> = 107
Age at MTX initiation, years, median (range)	49 (18:78)
Delay in MTX initiation, months, median (range)	18 (3:429)
Duration of MTX treatment, weeks, median (range)	49 (4:261)
Maximum MTX dose, mg/week, median (range)	15.0 (5.0:30.0)
Mean MTX dose, mg/week, median (range)	15.0 (5.0:26.9)
Route of administration	
Oral	90 (84.1)
Subcutaneous	2 (1.9)
Switch <sup>a</sup>	15 (14.0)
Systemic corticosteroids, <i>n</i> (%)	37 (34.6)
Folic acid, <i>n</i> (%)	78 (72.9)

<sup>a</sup>Switch from oral to subcutaneous administration. Reason for switching were side-effects in 4 patients or lacking efficacy in the remaining 11 patients.

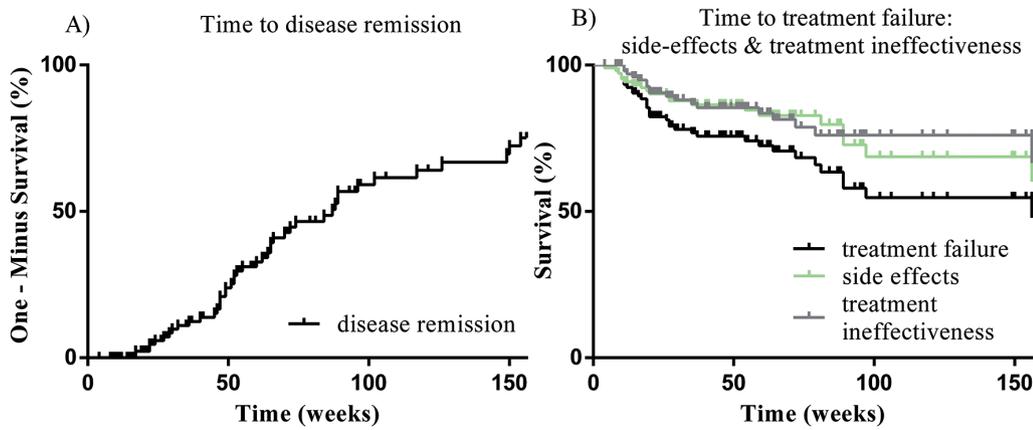


Fig. 1. (a) Methotrexate (MTX) time to disease remission curves in 107 patients with localized scleroderma. (b) MTX survival curves related to treatment failure (black line) segregated into side-effects (green line) and treatment ineffectiveness (grey line).

fatigue ( $n=3$ , 2.8%), pulmonary symptoms suspected of being related to MTX ( $n=3$ ), renal impairment ( $n=1$ , 0.9%), depression ( $n=1$ , 0.9%) and headache ( $n=1$ , 0.9%). Finally, 12 (11.2%) patients were lost to follow-up, 13 (12.2%) were still being treated at data lock and 4 (3.7%) had other reasons for treatment discontinuation (i.e. patient's wish, elective surgery).

*Drug survival of methotrexate*

Fig. 1a shows the one minus drug survival curve for MTX related to disease remission. After 1 year, 25.3% of patients stopped MTX because of disease remission. After 2 years this proportion was 62.5%. The median time to discontinuation of MTX due to disease remission was 87 weeks. Fig. 1b shows drug survival related to treatment failure. After 1 and 2 years, drug survival related to treatment failure was 75.7% and 54.7%, respectively. Subanalyses of drug survival related to the separated discontinuation reasons adverse events and ineffectiveness showed no significant differences.

*Selection of candidate predictors of drug survival*

Table S1<sup>1</sup> displays the HRs and 95% CIs for the univariate Cox regression analysis for all the variables tested.

<sup>1</sup><http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2411>

The variables with a  $p$ -value  $\leq 0.2$  in the univariate analysis were put into the multivariate model.

*Predictors of drug survival in localized scleroderma: disease remission*

Forty-eight patients discontinued MTX due to disease remission, which allowed us to add 5 predictors of interest in a multivariate model. Univariate analysis identified age at MTX initiation ( $p=0.004$ , HR 1.144 (95% CI 1.043–1.255)), absence of other autoimmune diseases ( $p=0.004$ , HR 3.636 (95% CI 1.153–8.696)), absence of deep LoS ( $p=0.007$ , HR 5.155 (95% CI 1.572–16.949)), absence of administration of folic acid ( $p=0.00$ , HR 5.051 (95% CI 2.660–9.615)) and the calendar year of MTX initiation ( $p=0.000$ , HR 0.859 (95% CI 0.81–0.909)) as possible predictors. Fig. 2 shows the HRs and 95% CIs resulting from the multivariate analysis. The following 3 variables remained statistically significant in a multivariable model: the calendar year of MTX initiation was associated with a drug survival related to disease remission (HR 0.865 (95% CI 0.814–0.919)). In other words, more recent MTX initiation, measured as a more recent calendar year, was associated with decreased drug survival due to disease remission. More interestingly, patients who only had LoS showed better drug survival related to disease remission compared with patients with

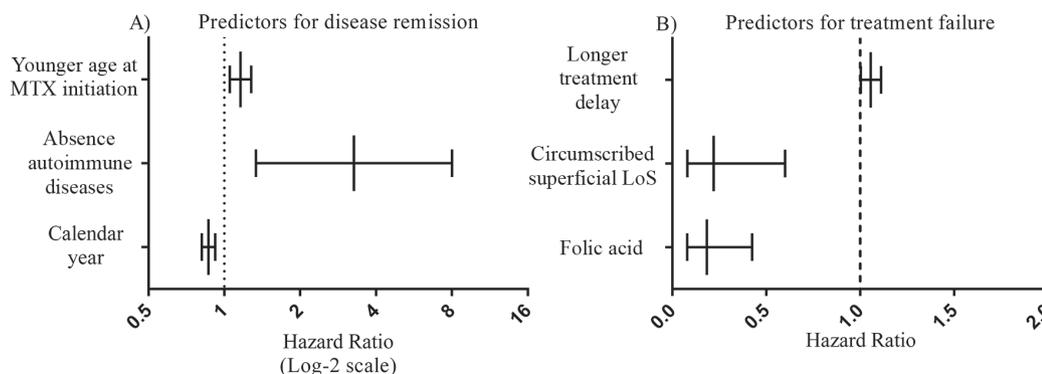


Fig. 2. Predictors of methotrexate (MTX) drug survival in 107 patients with localized scleroderma, segregated for treatment discontinuation reasons (a) disease remission and (b) treatment failure. Displayed are hazard ratios and their confidence intervals resulted from multivariate Cox regression analyses. The x-axis in panel a is a log-2 scale.

multiple autoimmune diseases (HR 3.268 (95% CI 1.334–8.009)). Finally, younger age (up to 18 years of age) at MTX initiation was associated with increased drug survival related to disease remission (HR 1.159 (95% CI 1.052–1.277)).

#### *Predictors of drug survival: treatment failure*

Thirty-four patients discontinued MTX due to treatment failure, which allowed us to add 3 predictors of interest to the multivariate model. Univariate analysis identified the delay in treatment initiation ( $p=0.079$ , HR 1.044 (95% CI 0.995–1.096)), having circumscribed superficial LoS ( $p=0.020$ , HR 0.370 (95% CI 0.160–0.854)) and receiving folic acid ( $p=0.006$ , HR 0.368 (95% CI 0.180–0.735)) as possible predictors. All 3 predictors remained significant in the multivariable model, leading to the following HRs and their interpretation: patients who received folic acid (HR 0.184 (95% CI 0.079–0.425)) and patients with circumscribed superficial LoS (HR 0.221 (95% CI 0.081–0.601)) were protected against treatment failure. On the other hand, patients with a longer treatment initiation delay (HR 1.056 (95% CI 1.004–1.112)) were at greater risk for treatment failure.

Subanalyses of MTX discontinuation due to side-effects and treatment ineffectiveness were restricted to multivariable models with 2 predictors due to the relatively low number of events for these 2 stopping reasons separately (20 and 18 events, respectively). Receiving folic acid (HR 0.279 (95% CI 0.101–0.773)) protected against side-effects, whereas patients with a prolonged treatment initiation delay (HR 1.076 (95% CI 1.014–1.142)) were at greater risk of stopping due to side-effects. Patients with a longer treatment initiation delay were also at greater risk of stopping MTX due to treatment ineffectiveness (HR 1.057 (95% CI 1.000–1.117)).

## DISCUSSION

In this study 26% and 63% of patients stopped MTX due to disease remission after one and two years, respectively. The median time to MTX discontinuation due to disease remission was 87 weeks. Drug survival related to treatment failure was 76% after one year. Thus, 24% of patients stopped MTX within one year because of side-effects or treatment ineffectiveness. It is difficult to compare these results with those of other studies, as the current study presents the first data regarding drug survival of MTX in LoS. Most previous studies describing MTX in LoS focus on a paediatric population (13–19). Only 3 original papers have described MTX as a treatment option in adult patients; Seyger et al. (8) reported a beneficial effect of MTX in 6 out of 9 patients after 24 weeks. Kreuter et

al. (10) reported a beneficial effect of MTX in combination with pulsed intravenous methylprednisolone in 14 out of 15 patients. Finally, Kroft et al. (9) reported remission rates of 51% and 73% for MTX mono- and combination therapy with prednisone in a cohort that contained sclerotic diseases other than LoS (49 with LoS, 5 with eosinophilic fasciitis, 2 scleroderma diabeticorum and 2 scleromyxoedema).

In contrast to publications on LoS studies, drug survival studies have been reported more frequently in other diseases. However, in most diseases, remission is not a reason to stop treatment. Shalom et al. (20) presented drug survival rates of MTX of only 59.3% after one year in 2,632 patients with psoriasis. Thus, 40.7% of subjects stopped treatment within one year. However, the lack of detailed description of the reasons for discontinuation in this study means that it is difficult to compare this study with our results.

With regards to predictors of drug survival, we showed that younger age at treatment initiation was associated with higher rates of disease remission. A possible explanation could be that older patients are more frequently affected by comorbidities, which may lower the chance of treatment success. Secondly, not being affected by other autoimmune diseases also increased the chance of achieving disease remission. The group of patients with other autoimmune diseases might reflect a group of patients with more severe forms of the disease. Furthermore, we identified an association between calendar year at MTX initiation and disease remission. A possible explanation for this association could be changing prescription behaviour, as this analysis contains treatment episodes from the early 1990s. Treatment has become more aggressive during the years; partly due to increased experience with MTX and partly due to literature advocating prolonged treatment with MTX in LoS (18, 21).

Regarding treatment failure, we show that folic acid protected against treatment failure (HR 0.184). The protective effect of folic acid against side-effects caused by MTX is well known in other diseases, such as rheumatic diseases and psoriasis (22–24). These findings, in combination with scarcity of alternative treatments for MTX in LoS, emphasize the necessity for the prescription of folic acid to decrease the likelihood of MTX failure. Secondly, our results imply that more severe disease subtypes (i.e. the linear or deep subtypes) are more difficult to treat successfully, as the milder superficial subtype was associated with a lower risk of treatment failure compared with the severe subtypes. Most interestingly, we showed that patients with a longer delay in MTX initiation were at greater risk of stopping MTX due to treatment failure. These data suggest that early treatment, as is desired in other diseases, such as rheumatoid arthritis, is also preferred in LoS (25–27).

A limitation of this study is its retrospective design. Secondly, the study is limited by the relatively low number of events, which prevented us from performing certain subgroup analyses. However, we maximized the number of candidate predictors for each multivariable model, based on the number of events in that model. Finally, we investigated associations between predictors and outcomes and not causality. Further replication of these data is needed to investigate causations between the predictors and outcomes identified in this study.

In conclusion, this is the first study to present data regarding drug survival and predictors for drug survival of MTX in adults with LoS in a large daily practice cohort. This study shows that 26% and 63% of patients stopped MTX due to disease remission after one and two years, respectively. Younger patients and those without other autoimmune diseases more frequently stopped MTX due to disease remission. In addition, 24% of patients stopped MTX due to treatment failure within one year. With regards to minimizing treatment failure, adding folic acid and a reduction in treatment delay might be the most important factors in clinical practice.

*The authors declare no conflicts of interest.*

## REFERENCES

- Fett N, Werth VP. Update on morphea: part I. Epidemiology, clinical presentation, and pathogenesis. *J Am Acad Dermatol* 2011; 64: 217–228; quiz 229–230.
- Kreuter A. Localized scleroderma. *Dermatol Ther* 2012; 25: 135–147.
- Kroft EB, de Jong EM, Evers AW. Psychological distress in patients with morphea and eosinophilic fasciitis. *Arch Dermatol* 2009; 145: 1017–1022.
- Klimas NK, Shedd AD, Bernstein IH, Jacobe H. Health-related quality of life in morphea. *Br J Dermatol* 2015; 172: 1329–1337.
- Zwischenberger BA, Jacobe HT. A systematic review of morphea treatments and therapeutic algorithm. *J Am Acad Dermatol* 2011; 65: 925–941.
- Fett N, Werth VP. Update on morphea: part II. Outcome measures and treatment. *J Am Acad Dermatol* 2011; 64: 231–242; quiz 243–234.
- Kreuter A, Krieg T, Worm M, Wenzel J, Gambichler T, Kuhn A, et al. AWMF-Leitlinie Nr. 013/066 Diagnostik und Therapie der zirkumskripten Sklerodermie. *J Dtsch Dermatol Ges* 2009; 7 Suppl 6: S1–14.
- Seyger MM, van den Hoogen FH, de Boo T, de Jong EM. Low-dose methotrexate in the treatment of widespread morphea. *J Am Acad Dermatol* 1998; 39: 220–225.
- Kroft EB, Creemers MC, van den Hoogen FH, Boezeman JB, de Jong EM. Effectiveness, side-effects and period of remission after treatment with methotrexate in localized scleroderma and related sclerotic skin diseases: an inception cohort study. *Br J Dermatol* 2009; 160: 1075–1082.
- Kreuter A, Gambichler T, Breuckmann F, Rotterdam S, Freitag M, Stuecker M, et al. Pulsed high-dose corticosteroids combined with low-dose methotrexate in severe localized scleroderma. *Arch Dermatol* 2005; 141: 847–852.
- van den Reek JM, Kievit W, Gniadecki R, Goeman JJ, Zweegers J, van de Kerkhof PC, et al. Drug survival studies in dermatology: principles, purposes, and pitfalls. *J Invest Dermatol* 2015; 135: e34.
- Laxer RM, Zulian F. Localized scleroderma. *Curr Opin Rheumatol* 2006; 18: 606–613.
- Weibel L, Sampaio MC, Visentin MT, Howell KJ, Woo P, Harper JI. Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphea) in children. *Br J Dermatol* 2006; 155: 1013–1020.
- Fitch PG, Rettig P, Burnham JM, Finkel TH, Yan AC, Akin E, et al. Treatment of pediatric localized scleroderma with methotrexate. *J Rheumatol* 2006; 33: 609–614.
- Cox D, G OR, Collins S, Byrne A, Irvine A, Watson R. Juvenile localised scleroderma: a retrospective review of response to systemic treatment. *Ir J Med Sci* 2008; 177: 343–346.
- Tollefson MM, Witman PM. En coup de sabre morphea and Parry-Romberg syndrome: a retrospective review of 54 patients. *J Am Acad Dermatol* 2007; 56: 257–263.
- Piram M, McCuaig CC, Saint-Cyr C, Marcoux D, Hatami A, Haddad E, et al. Short- and long-term outcome of linear morphea in children. *Br J Dermatol* 2013; 169: 1265–1271.
- Torok KS, Arkachaisri T. Methotrexate and corticosteroids in the treatment of localized scleroderma: a standardized prospective longitudinal single-center study. *J Rheumatol* 2012; 39: 286–294.
- Zulian F, Martini G, Vallongo C, Vittadello F, Falcini F, Patrizi A, et al. Methotrexate treatment in juvenile localized scleroderma: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2011; 63: 1998–2006.
- Shalom G, Zisman D, Harman-Boehm I, Biterman H, Greenberg-Dotan S, Polishchuk I, et al. Factors associated with drug survival of methotrexate and acitretin in patients with psoriasis. *Acta Derm Venereol* 2015; 95: 973–977.
- Zulian F, Vallongo C, Patrizi A, Belloni-Fortina A, Cutrone M, Alessio M, et al. A long-term follow-up study of methotrexate in juvenile localized scleroderma (morphea). *J Am Acad Dermatol* 2012; 67: 1151–1156.
- van Ede AE, Laan RF, Rood MJ, Huizinga TW, van de Laar MA, van Denderen CJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2001; 44: 1515–1524.
- Shea B, Swinden MV, Tanjong Ghogomu E, Ortiz Z, Katchamart W, Rader T, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *Cochrane Database Syst Rev* 2013; 5: Cd000951.
- Duhra P. Treatment of gastrointestinal symptoms associated with methotrexate therapy for psoriasis. *J Am Acad Dermatol* 1993; 28: 466–469.
- Verstappen SM, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, Borg EJ, et al. Five-year follow-up of rheumatoid arthritis patients after early treatment with disease-modifying antirheumatic drugs versus treatment according to the pyramid approach in the first year. *Arthritis Rheum* 2003; 48: 1797–1807.
- Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum* 2002; 46: 347–356.
- McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med* 2011; 365: 2205–2219.