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CLINICAL ARTICLE

Effect of disease-modifying anti-rheumatic drugs on therapeutic outcomes among women with endometriosis ☆

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Synopsis: Among women with endometriosis, treatment with disease-modifying anti-rheumatic drugs for at least 6 weeks was associated with a lower frequency of opioid usage.

Abstract

Objective: To determine whether disease-modifying anti-rheumatic drugs (DMARDs) affect the use of hormonal treatments, subsequent ablative surgery, and need for pain management, including opioids, non-steroidal anti-inflammatory drugs and anti-depressants, among women with endometriosis.

Methods: In a retrospective study, data were reviewed from women with surgically confirmed endometriosis who were not treated (n=234) or treated with DMARDs for 6 weeks or more (n=25) before surgical diagnosis at a single healthcare system in the USA between 2003 and 2013. The postoperative use of hormonal treatments, proportion of women undergoing subsequent ablative surgery, and use of adjunct therapies such as antidepressants, steroids, and opioids after surgery were compared between the two groups.

Results: The two groups showed differences in age (P=0.007) and follow-up time (P<0.001). Univariate analysis showed more frequent use of hormonal treatments (P=0.045) and antidepressants (P=0.006) among women treated with DMARDs. The frequency of post-diagnostic use of opioids was lower among treated women (P=0.001); this association remained significant in multivariate analysis controlling for potential confounders (P=0.003).

Conclusion: The findings suggest that administration of DMARDs for at least 6 weeks is associated with decreased opioid usage among women with endometriosis.

1 INTRODUCTION

Endometriosis is a gynecologic condition that affects approximately 5%–15% of women of reproductive age in the USA [1]. The prevailing theory behind the pathogenesis of endometriosis is Sampson's theory of retrograde menstruation. Recent work has indicated that more than 90% of women of reproductive age experience retrograde menstruation; however, only a small fraction of them develop endometriosis [1]. This indicates that either there is a factor that enhances implantation or there is a defect in clearance of menstrual remnants. Furthermore, it suggests that a component of the pathogenesis of endometriosis that is linked to a defect in the clearance of menstrual remnants by the immune system.

Endometriosis meets the general criteria defined for an autoimmune disease, including multiple abnormalities in T and B cell function and various auto-antibodies [2-6]. Although no relationship has been found between endometriosis and autoimmune diseases such as systemic lupus erythematosus and Sjogren syndrome, an association with inflammatory bowel disease has been reported [7, 8]. In addition, the underlying immune dysfunction that leads to the persistence of endometriosis remains unresolved. Evidence indicates that the cytotoxic activity of natural killer cells is decreased and the innate immune system is unable to react sufficiently to endometriotic implants [9-10]. In addition to this deficiency in reacting to and destroying the endometriotic implants, these immune cells produce pro-inflammatory factors that can enhance the growth of endometriotic implants [11]. This relationship suggests that immune suppression might play a role in not only reducing the spread of endometriosis, but also possibly reversing the damage caused by it.

One method of examining this issue is to study the use of immunosuppressants such as disease-modifying anti-rheumatic drugs (DMARDs). These drugs can be classified as “synthetic” (e.g., hydroxychloroquine and methotrexate) and “biologic” (antibody-based; e.g., etanercept and infliximab). Prospective studies in baboons found that immunosuppressants had no effect on the anatomic progression of endometriosis (assessed via the size of endometriotic implants) as compared with placebo [12]. Initial studies in humans examined the effect of pentoxifylline, a phosphodiesterase inhibitor used to treat rheumatoid arthritis. In four studies involving 334 women, no significant effect was seen on either pain reduction or infertility [13]. One study [14] showed an improvement in endometriotic implants in vitro with 5-fluorouracil, whereas another [15] indicated no significant quality of life improvement (based upon Biberoglu–Behrman and visual analogue pain scores) after treatment with the TNFα inhibitor, infliximab. However, those studies with sample sizes of 10–21 women were underpowered to detect small improvements. The aim of the present study was therefore to examine further whether immunosuppressants can affect the course of endometriosis and offer a viable treatment option.

2 MATERIALS AND METHODS

In a retrospective study, data were reviewed from women who were treated for endometriosis at a single healthcare system in Cleveland, OH, USA, between January 1, 2003, and January 1, 2014. The study was approved by the Women’s Health Institute and the institutional review board of the Cleveland Clinic. Informed consent was not deemed necessary because it was a retrospective study and all patient information was de-identified.

Study information was extracted from the institution's electronic medical record. The data review was performed by using the International Classification of Disease (ninth edition) codes for endometriosis (657.0 and 657.1), focusing on women of reproductive age (18–50 years) with surgical evidence of endometriosis. Women who did not undergo surgery for the diagnosis of endometriosis were excluded.

The women identified in the initial search were further searched for those who were undergoing treatment with a DMARD such as methotrexate, leflunomide, hydroxychloroquine, mycophenolate mofetil, or biologic (e.g., etanercept, infliximab, trastuzumab, or rituximab). All women who were treated with these DMARDs had a pre-existing rheumatologic disease, and were included in the present study only if they had undergone DMARD treatment for at least 6 weeks. The remaining women with endometriosis were eligible for inclusion in the control group and simple random sampling of patient charts was used to identify the control group patients. Women of non-reproductive age, those undergoing chemotherapy or radiation therapy for malignancy, transplant patients, and women with any congenital or acquired immune-deficiency were excluded. Patients were excluded from the control group if they had any history of rheumatologic disease.

The study was designed to detect a 50% difference in outcomes between the DMARD-treated and untreated groups under the assumption of a null difference in proportion of 10%. The power was set at 80% with an α value of 0.05, which indicated that 20 women were required in each treatment group.

The data extracted from the medical charts included age, ethnicity, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), parity, time of diagnostic surgery, presence of infertility, presence of rheumatic disease, and type of DMARD used for treatment. In addition, information on the stage of endometriosis and duration of total follow-up since the first diagnostic surgery was collected.

The primary outcomes included the total number of ablative surgeries for endometriosis (laparoscopic or open) and the use of any hormonal suppression (i.e., medroxyprogesterone acetate, levonorgestrel intra-uterine devices (IUDs) or leuprolide acetate). Oral contraceptive pills were not included as an outcome measure given the prevalence of their use for contraception and because women taking DMARDs may also take oral contraception owing to the teratogenicity of many DMARDs. The secondary outcomes included the use of any adjunctive pain therapy such as anti-depressants, gabapentin, systemic steroids, and opioids.

SAS software version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses. Continuous variables were presented as mean ± SD. Categoric variables were presented as number (percentage). A two-sample *t* test was used to assess differences in continuous variables between untreated and treated women. Pearson χ^2 test or Fisher exact test was used to assess differences in categoric measures. Logistic regression was performed as part of the multivariate analysis. All tests were performed at a significance level of 0.05.

3 RESULTS

The database search identified 703 women diagnosed with endometriosis during the study period. Of these women, 27 were exposed to at least one DMARD for 6 weeks or longer. For the control group, 237 patient charts for women with surgically confirmed endometriosis and no history of DMARD exposure were selected using simple random sampling (Figure 1). Chart review was discontinued past this point because this sample size represented more than five times the number of charts required to adequately power the study. Five charts were subsequently excluded on the basis of insufficient data on follow-up after diagnostic surgery (DMARD group, n=2; untreated group, n=3).

The demographic characteristics of the study population by DMARD exposure are presented in Table 1. The two groups showed differences in age (P=0.007) and duration of follow-up (P<0.001). The two groups did not differ in BMI, ethnicity, presence of infertility, endometriosis stage, or type of diagnostic surgery.

Among the 25 women exposed to DMARDs, all had received this treatment for a rheumatologic disorder, the most common of which was rheumatoid arthritis (17; 68%) followed by systemic lupus erythematosus (7; 28%). The most common DMARD used was hydroxychloroquine (10; 40%), followed by methotrexate (3; 12%). The remaining women were treated with various other DMARDs, including leflunomide, mycophenolate mofetil, and biologics (etanercept and infliximab).
In univariate analysis, there was no difference between the DMARD-treated and untreated groups in the frequency of additional ablative surgery (laparoscopic or open) after the initial diagnostic surgery (P=0.16) or in the use of hormonal

suppressive therapies such as IUDs (*P*=0.48) or leuprolide acetate (*P*=0.68). However, there was a higher frequency of medroxyprogesterone acetate usage among women treated with DMARDs than among untreated women (*P*=0.045) (Table 2).

In terms of secondary outcomes, there was a higher frequency of corticosteroid (*P*=0.012) and antidepressant (*P*=0.006) usage, and a lower frequency of total opioid usage (16.0% vs 50.4%; *P*=0.001) in the DMARD-treated group than in the untreated group (Table 3).

Multivariate analysis including age at diagnosis, ethnicity (white vs non-white), BMI, duration of follow-up after diagnostic surgery, and type of diagnostic surgery confirmed that usage of levonorgestrel IUDs and leuprolide acetate were not significantly associated with DMARD treatment (data not shown). When the model was corrected for all of the above factors, medroxyprogesterone acetate usage (Table 4) and corticosteroid usage (Table 5) were no longer significantly associated with DMARD treatment. However, the likelihood of antidepressant usage remained significantly higher (*P*=0.010) (Table 6) and that of opioid usage remained significantly lower (*P*=0.003) (Table 7) for women treated with DMARDs than for untreated women.

4 DISCUSSION

The present study found no significant difference in the proportion of women who underwent subsequent ablative surgery or received hormonal treatment (levonorgestrel IUDs or leuprolide acetate) between women who received DMARD

treatment and those who did not before surgically diagnosed endometriosis. However, it did show a higher frequency of antidepressant usage and a lower proportion of opioid usage among women who were treated with DMARDs.

Notably, the average age of the DMARD-treated and untreated groups differed, which raises the question of whether symptomatology for endometriosis varies with age and, if so, might influence opioid usage. In a prospective study of 35 women ranging from 18 to 53 years, all participants reported similar symptoms of dyspareunia and dysmenorrhea, albeit with varying distributions [17]. Furthermore, a recent retrospective review of over 23 000 individuals on the Medicaid program in the USA did not find a relationship between age and chronic opioid usage among patients with rheumatologic conditions [18]. In the present multivariate analysis, the association between DMARD treatment and both antidepressant and opioid use remained significant even after adjusting for potential confounders such as age, duration of follow-up, ethnicity, and performance of hysterectomy at the time of diagnosis of endometriosis.

To our knowledge, this is the first retrospective study to examine the effect of DMARD usage among women with endometriosis. Nevertheless, it has limitations, including those inherent to a retrospective study. First, data collection was limited to one hospital system and relied on the accuracy of documentation in the electronic medical record. Second, to determine the number of hormonal or non-hormonal treatments taken by the study women, the total number of prescriptions were counted for each of the therapies; however, it was not possible to confirm that the medications were taken in their entirety. Last, it was not possible to analyze the type

of endometriotic lesions observed, such as superficial endometriosis, diffuse infiltrating endometriosis, and ovarian endometrioma, owing to the paucity of these data in the medical record.

The strengths of the study include its use of data from multiple hospitals from a single healthcare system spanning more than a decade since the introduction of an electronic medical record in the Cleveland Clinic health system. In addition, this study examined the number of total interventions used after surgical diagnosis of endometriosis in contrast to previous studies in which pain scores were used to assess response to treatment (e.g. Koninckx et al. [15]). Such pain scores do not consistently give a reliable assessment of pain as a measure of disease burden and/or stage of endometriosis [19].

The association between DMARD treatment and anti-depressant usage observed in the present study is consistent with prior studies. Women with endometriosis are more likely to experience psychiatric disturbances; however, it remains to be determined whether this results from the endometriosis, chronic pelvic pain, or inflammation, or from a combination of all three [20]. Women with autoimmune diseases are also at an increased risk of developing depression, with more than 38% of those with rheumatoid arthritis exhibiting this condition [21]. The presence of autoimmune disease in the cohort of women treated with DMARDs might be an underlying factor in the increased use of antidepressants. In a cross-sectional study by Jamshidi et al. [22], however, no association was found between the severity of rheumatoid arthritis, as measured by the disease activity score, and the severity of a patient's depression. Unfortunately, few of the present study women had

documented disease activity scores. On the basis of the multivariate analysis, the difference in antidepressant usage between the DMARD-treated and untreated groups might also have been influenced by the type of initial diagnostic surgery that the woman underwent, with those undergoing hysterectomy approximately twice as likely to use antidepressants. Given the limited information in the medical record, it was difficult to assess whether this relationship was further influenced by pre-existing chronic pain or was a consequence of morbidity from a major surgery such as hysterectomy.

A notable finding from the present study is the lower frequency of opioid usage among women exposed to DMARDs, which remained significant after multivariate analysis. Opioid usage, especially for the treatment of chronic pain, is an increasing public health concern. Studies have demonstrated a correlation between the sale of opioids and the risk of death, and efforts are increasing to find ways to mitigate opioid usage [23]. The present finding that DMARD treatment among women with endometriosis was associated with lower opioid usage might help to develop new approaches to limiting opioid usage among women with chronic pain secondary to endometriosis. DMARDs, both as a monotherapy and as part of a combined regimen, have been shown to decrease pain for patients with various rheumatic conditions [24]. It might be speculated that this is secondary to a decrease in pain owing to reduced inflammation; however, to our knowledge, no studies have addressed the exact mechanism of pain control by DMARDs in general.

The lower frequency of chronic opioid usage is also unexpected given the relationship between rheumatologic conditions and depression. As mentioned above, depressive disorders are seen more often among patients with rheumatologic conditions [21]. In addition, a retrospective analysis of more than 39 000 individuals found an increased association of chronic opioid usage among those who used selective serotonin reuptake inhibitors [25]. Therefore, the decreased proportion of chronic opioid usage among the women taking DMARDs in the present study remains unexpected and worth further investigation.

A subgroup analysis was not possible given the limited number of women receiving each type of synthetic DMARD; however, future studies might include a larger cohort of women exposed to DMARDs to facilitate additional stratification by type of DMARD. Future research should also include prospective trials to assess the effect of DMARDs on pain control among women with endometriosis, especially synthetic DMARDs such as hydroxychloroquine and methotrexate.

Author contributions

AK contributed to project design, chart review, statistical analysis, and manuscript preparation. SS participated in chart review and manuscript preparation. XL contributed to the statistical analysis and manuscript preparation. TF participated in project design and manuscript preparation.

Conflicts of interest

The authors have no conflicts of interest.

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Figure 1 Flow chart showing selection of the study population.

Table 1 Characteristics of the study women by DMARD treatment

Characteristic	Overall (n=259)	DMARD usage		
		No (n=234)	Yes (n=25)	*P* value
Age at diagnosis, y				0.007 [b]
Mean ± SD	36.9 ± 7.4	36.5 ± 7.5	40.7 ± 5.5	
Median (range)	37.3 (19.0–49.7)	36.8 (19.0–49.7)	41.1 (30.0–48.7)	
Q1, Q3	31.3, 43.0	30.9, 42.7	37.0, 44.8	
BMI [a]				0.735 [b]
Mean ± SD	36.9 ± 166.4	38.1 ± 175.1	26.0 ± 5.0	
Median (range)	25.4 (12.8–2640.0)	25.5 (12.8–2640.0)	24.9 (17.9–38.0)	
Q1, Q3	21.3, 30.4	21.0, 30.4	22.6, 30.0	
Follow-up, mo [a]				<0.001 [b]
Mean ± SD	24.3 ± 28.2	21.6 ± 25.7	49.3 ± 37.4	
Median (range)	13.0 (0.1–139.0)	12.0 (0.1–115.0)	36.0 (3.0–139.0)	
Q1, Q3	1.0, 36.0	1.0, 36.0	25.0, 70.0	
Caucasian				0.42 [c]
Yes	203 (78.4)	185 (79.1)	18 (72.0)	
No	56 (21.6)	49 (20.9)	7 (28.0)	
Infertility				0.24 [c]
No	217 (83.8)	194 (82.9)	23 (92.0)	
Yes	42 (16.2)	40 (17.1)	2 (8.0)	
Endometriosis stage				0.068 [c]
0–2	232 (90.3)	212 (91.4)	20 (80.0)	
3–4	25 (9.7)	20 (8.6)	5 (20.0)	
Ethnicity				0.48 [d]
White	203 (78.4)	185 (79.1)	18 (72.0)	
Hispanic/Latino	21 (8.1)	19 (8.1)	2 (8.0)	
African–American	26 (10.0)	21 (9.0)	5 (20.0)	
Asian/Pacific Islander	4 (1.5)	4 (1.7)	0 (0)	
Other	5 (1.9)	5 (2.1)	0 (0)	

Abbreviations: DMARD: disease-modifying anti-rheumatic drug.
[a] Data were available on BMI for 247 (overall), 223 (untreated), and 24 (treated) women, and on follow-up for 258 (overall), 233 (untreated), and 25 (treated) women.
[b] By *t* test.
[c] By Pearson χ^2 test.
[d] By Fisher exact test.

Table 2 Primary outcomes among the study women by DMARD treatment

Outcome	Overall (n=259)	DMARD usage		*P* value [a]
		No (n=234)	Yes (n=25)	
Ablative surgery				0.16
No	239 (62.9)	219 (65.4)	20 (40.0)	
Yes	31 (37.1)	26 (34.6)	5 (60.0)	
IUD				0.48
No	245 (95.0)	222 (95.3)	23 (92.0)	
Yes	13 (5.0)	11 (4.7)	2 (8.0)	
MPA				0.045
No	242 (93.4)	221 (94.4)	21 (84.0)	
Yes	17 (6.6)	13 (5.6)	4 (16.0)	
Leuprolide acetate				0.68
No	234 (90.3)	212 (90.6)	22 (88.0)	
Yes	25 (9.7)	22 (9.4)	3 (12.0)	

Abbreviations: DMARD, disease-modifying anti-rheumatic drug; MPA, medroxyprogesterone acetate; IUD, intrauterine device.
[a] By *t* test.

Table 3 Secondary outcomes among the study women by DMARD treatment

Outcome	Overall (n=259)	DMARD usage		*P* value [a]
		No (n=234)	Yes (n=25)	
Steroid usage				0.012
No	163 (62.9)	153 (65.4)	10 (40.0)	
Yes	96 (37.1)	81 (34.6)	15 (60.0)	
Antidepressant usage				0.006
No	168 (64.9)	158 (67.5)	10 (40.0)	
Yes	91 (35.1)	76 (32.5)	15 (60.0)	
NSAID usage				0.19
No	65 (25.1)	56 (23.9)	9 (36.0)	
Yes	194 (74.9)	178 (76.1)	16 (64.0)	
Gabapentin usage				0.51
No	237 (91.5)	215 (91.9)	22 (88.0)	
Yes	22 (8.5)	19 (8.1)	3 (12.0)	
Opioid usage				0.001
No	137 (52.9)	116 (49.6)	21 (84.0)	
Yes	122 (47.1)	118 (50.4)	4 (16.0)	

Abbreviations: DMARD, disease-modifying anti-rheumatic drug; NSAID, nonsteroidal anti-inflammatory drug.
[a] By Pearson χ^2 test.

Table 4 Multivariate analysis for the likelihood of MPA usage**.**

Factor	Odds ratio (95% CI)	*P* value
DMARD, yes vs no	4.274 (0.98–18.628)	0.053
Age at diagnosis, y	0.959 (0.888–1.036)	0.29
White, yes vs no	1.128 (0.289–4.407)	0.86
BMI, per 1-unit increase	0.985 (0.894–1.084)	0.75
Duration of follow-up, mo	1.016 (0.998–1.034)	0.082
Surgery, hysterectomy vs non hysterectomy	0.249 (0.049–1.266)	0.094

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; MPA, medroxyprogesterone acetate.

Table 5 Multivariate analysis for the likelihood of steroid usage.

Factor	Odds ratio (95% CI)	*P* value
DMARD, yes vs no	1.781 (0.705–4.501)	0.22
Age at diagnosis, y	1.026 (0.988–1.066)	0.18
White, yes vs no	0.594 (0.309–1.142)	0.12
BMI, per 1-unit increase	0.993 (0.951–1.037)	0.76
Duration of follow-up, mo	1.01 (1.000–1.021)	0.057
Surgery, hysterectomy vs non-hysterectomy	1.098 (0.617–1.954)	0.75

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; DMARD, disease-modifying anti-rheumatic drugs.

Table 6 Multivariate analysis for the likelihood of antidepressant usage.

Factor	Odds ratio (95% CI)	*P* value
DMARD, yes vs no	3.525 (1.361–9.130)	0.010
Age at diagnosis	0.982 (0.946–1.021)	0.36
Caucasian, yes vs no	1.322 (0.659–2.652)	0.43
BMI, per 1 unit increase	1.002 (0.996–1.008)	0.48
Duration of follow-up, mo	1.001 (0.990–1.012)	0.84
Surgery, hysterectomy vs non-hysterectomy	1.986 (1.120–3.522)	0.019

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug.

Table 7 Multivariate analysis for the likelihood of opioid usage.

Factor	Odds ratio (95% CI)	*P* value
DMARD, yes vs no	0.165 (0.051–0.532)	0.003
Age at diagnosis, y	1.000 (0.965–1.036)	>0.99
White, yes vs no	1.057 (0.551–2.031)	0.87
BMI, per 1-unit increase	1.002 (0.993–1.011)	0.68
Duration of follow-up, mo	1.007 (0.996–1.018)	0.20
Surgery, hysterectomy vs non-hysterectomy	0.871 (0.500–1.517)	0.63

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug.