The Frequency and Distribution of Minocycline Induced Hyperpigmentation in a Rheumatoid Arthritis Population

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ABSTRACT. ***Objective.*** Minocycline is particularly useful in patients with rheumatoid arthritis (RA) with previous major sepsis, where anti-tumor necrosis factor is relatively contraindicated. Pigmentation is a documented side effect, but predisposing factors in an RA population have not been established. We investigated minocycline induced pigmentation in a population with RA to determine whether skin type and eye color influence predisposition to this side effect.

Methods. Patients with RA attending a rheumatology unit who had received minocycline were contacted by telephone and some were also interviewed in the clinic. Those receiving therapy for more than 3 months were assessed. Hair color, eye color, tendency to burn in the sun, and dose and duration of therapy were documented. The frequency, type, and distribution of pigmentation were established.

Results. Of 37 patients identified, 10 were excluded because the duration of therapy was less than 3 months. Of the remaining 27 patients, 85% were female, with median age 64 years (range 44–88) and median disease duration 23.5 years (range 4–51). Eleven patients (41%) developed pigmentation after a median of 12 months. Four of the 11 stopped their minocycline due to pigmentation. Hair color, eye color, and tendency to burn in the sun did not predict patients who developed pigmentation.

Conclusion. Pigmentation is a common side effect in patients receiving minocycline therapy for more than 3 months. Most patients do not stop therapy due to pigmentation. Those who stop are more likely to be female, less than 70 years of age, and have facial pigmentation. (First Release June 1 2006; J Rheumatol 2006;33:1254–7)

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Minocycline is a useful addition to the range of disease modifying antirheumatic drugs (DMARD) in the management of rheumatoid arthritis (RA), particularly in those with previous major sepsis, which is a contraindication to the introduction of anti-tumor necrosis factor therapy. Several randomized controlled trials of minocycline have shown benefit in reducing acute phase response and tender and swollen joint counts, although an effect on radiographic progression has been documented in only one study[1-6].

It has been assumed that minocycline represents a safer and less toxic alternative to other DMARD. The rate of side effects in randomized controlled trials was not higher than placebo. It has been noted, however, that in routine clinical practice dizziness is a frequent adverse effect, particularly early in the treatment course. Gradual dose increment often overcomes this problem. Hyperpigmentation has also been noted to occur more frequently in routine practice than was found in clinical trials[3]. Benign intracranial hypertension, drug induced systemic lupus erythematosus (SLE), and abnormal liver function tests can also occur, but are rare.

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Minocycline is used much more commonly in treatment of dermatological conditions, and the incidence of hyperpigmentation is more clearly established in this population. It is thought to occur in 2.4–5.7% of patients with acne vulgaris[7–9], and 28% of patients with rosacea[9]. It has been documented to affect the skin as well as the sclera, oral mucosa, ears, thyroid, teeth, nails, and breast milk[10-12]. Pigmentation is divided into 3 different types based on site of the pathological findings. Type I is characterized by blue-black macular pigmentation, which tends to be localized to sites of scarring or bruising[13]. Type II is seen as blue-black, brown, or slate grey macules on healthy skin, mainly on the shins or arms[14]. Type III is manifest as symmetrical muddy brown macules on healthy skin. Pigmentation is most visible on sun-exposed areas[14]. With type I pigmentation risk of development is thought to be independent of total cumulative dosage, while types II and III tend to develop in patients who have been treated with high doses for prolonged periods[14].

Minocycline is a yellow crystalline material that turns black on oxidation. Pigment formation probably occurs through polymerization in a process similar to melanogenesis from dopa. Minocycline is also capable of chelating with iron to form insoluble complexes[15]. Biopsies reveal pigment-laden macrophages in the dermis and subcutaneous fat, as well as extracellularly on collagen bundles and in adipocytes. Staining shows the presence of iron and melanin[16].

The frequency of pigmentation and predisposing factors

for the development of this adverse effect in RA has not yet been fully elucidated. Fair-skinned people are more at risk of cutaneous manifestations related to sun exposure, in particular cutaneous malignancy, and we wished to ascertain if fair skin was also a risk for the development of minocycline related pigmentation.

The aim of our study was to establish the frequency and type of minocycline induced pigmentation in an RA population.

MATERIALS AND METHODS

RA patients who attended the rheumatology unit and had received minocycline were contacted by telephone. All our patients are started on a dose of 50 mg twice daily, which is usually increased to 100 mg twice daily providing the drug has been well tolerated.

Information about dose and duration of minocycline therapy and details of any adverse effects, including dizziness, nausea, and pigmentation, were obtained. Patients with pigmentation were questioned in detail about the distribution, type, and time it took to develop, and whether the pigmentation had led to cessation of therapy. If treatment had been stopped it was noted whether the pigmentation had resolved. Further information was obtained from patients' case records. All affected patients were invited to the rheumatology clinic for further consultation and for the opportunity to photograph affected areas. Patients were then asked what information they had received regarding minocycline pigmentation prior to starting therapy and whether this would have affected their decision to commence treatment. Hair color, eye color, and tendency to burn in the sun were also documented. An attempt was made to correlate skin type and eye color to a tendency to develop skin pigmentation.

RESULTS

Twenty-seven patients who had received minocycline for more than 3 months were identified.

Demographic features. The median age was 64 years (range 44–80), median disease duration 23.5 years (range 4–51). Eighty-five percent were female and 85% were seropositive for rheumatoid factor.

Duration of treatment. Out of the 27 patients, 11 (41%) developed pigmentation after a median of 12 months (range 3 mo to 6 yrs). The median duration of therapy in the 16 patients who did not develop pigmentation was 12 months (range 3 mo to 3 yrs).

Drug dose. All patients had started minocycline at a dose of 50 mg twice daily. In 45% (5/11) of the pigmentation group and 75% (12/16) of the nonpigmentation group the dose had been increased to 100 mg twice daily after one month.

Prednisolone therapy. Two of 11 (18%) patients in the pigmentation group were taking low-dose prednisolone therapy (2.5 mg/day and 4 mg/day) compared with 2/16 (12.5%) patients in the nonpigmentation group (doses 5 mg/day and 4 mg/day). The median age in the pigmentation group was 62 years (range 49–72) and 64 years (range 45–80) in the nonpigmentation group.

Table 1 presents information on the type of pigmentation in each patient.

Four of the 11 patients (36%) stopped therapy due to pigmentation. All were female. In 2 there was evidence of facial pigmentation and 2 had arm pigmentation.

In Patient 1 the pigmentation had improved by 80% after discontinuing therapy 2 years previously (patient's own estimate), and in Patient 6 there was a 60% improvement after stopping minocycline 2 years ago (patient's estimate). Information since stopping minocycline was not available on Patients 2 and 11. Patient 4 stopped therapy due to lack of efficacy, and there was minimal improvement in skin changes over 6 months.

The 2 patients with facial pigmentation were referred to dermatology for laser therapy to resolve the pigmentation[17]. The patients stopping therapy due to arm pigmentation declined referral.

Nine patients had a further face-to-face consultation in addition to telephone consultation. Only 3 of these 9 patients were aware that skin pigmentation was a potential adverse effect of therapy prior to starting treatment, but all 9 said that knowledge of this would not have altered their decision to start treatment with minocycline as a DMARD. There was no correlation between skin type and eye and hair color and development of hyperpigmentation.

Figure 1 illustrates minocycline pigmentation observed in our population.

DISCUSSION

Minocycline induced pigmentation is common in an RA population, occurring in 41% in our cohort. All types of minocycline induced pigmentation were represented, with type II being most common. Pigmentation affecting the shins is very well tolerated by patients, with none stopping therapy for this reason. In our cool, Northern European climate legs are usually covered by clothing. Arm and facial pigmentation are more likely to result in discontinuation of therapy, particularly in younger female patients.

The median time to develop pigmentation was found to be 12 months, but it was possible to develop pigmentation at any time between 3 months and 6 years. The median duration of therapy in those who did not develop pigmentation was only 12 months, suggesting that the 41% incidence could increase with a longer followup period.

The incidence of pigmentation in RA is significantly higher than that reported in acne vulgaris, but closer to that expected in acne rosacea and pemphigus groups. Age has been postulated as a factor in the development of minocycline induced pigmentation, which may explain this difference, but we could not demonstrate a difference in median age between the 2 groups in our population. To conclude from our group that age is not a factor is not possible since the numbers of patients were small and there was a narrow age range. Minocycline pigmentation is known to affect skin that is abnormal — either scarred or thinned — which is often a feature of patients with RA, particularly those with severe disease; this is due to the drug therapy and the effect of the disease itself.

Table 1. Type of pigmentation and decision regarding therapy in patients with RA taking minocycline for 3 months or more.

Patient	Age, yrs	Sex	Type of Pigmentation	Type and Area of Pigmentation	Was Therapy Discontinued?	Time to Develop Pigmentation
1	62	F	I	Face sclera	Yes	6 yrs
2	71	F	II	Arms	Yes	6 mo
3	61	F	III	Arms, legs	No	6 mo
4	61	M	III	Generalized	No	1 yr
5	69	F	III	Generalized	No	3 mo
6	49	F	I and III	Face generalized	Yes	4 yrs
7	63	F	II	Legs	No	2 yrs
8	62	M	II	Sclera	No	2 yrs
9	64	M	II	Legs, face	No	1 yr
10	72	F	II	Arms	No	3 mo
11	52	F	II	Arms	Yes	3 mo

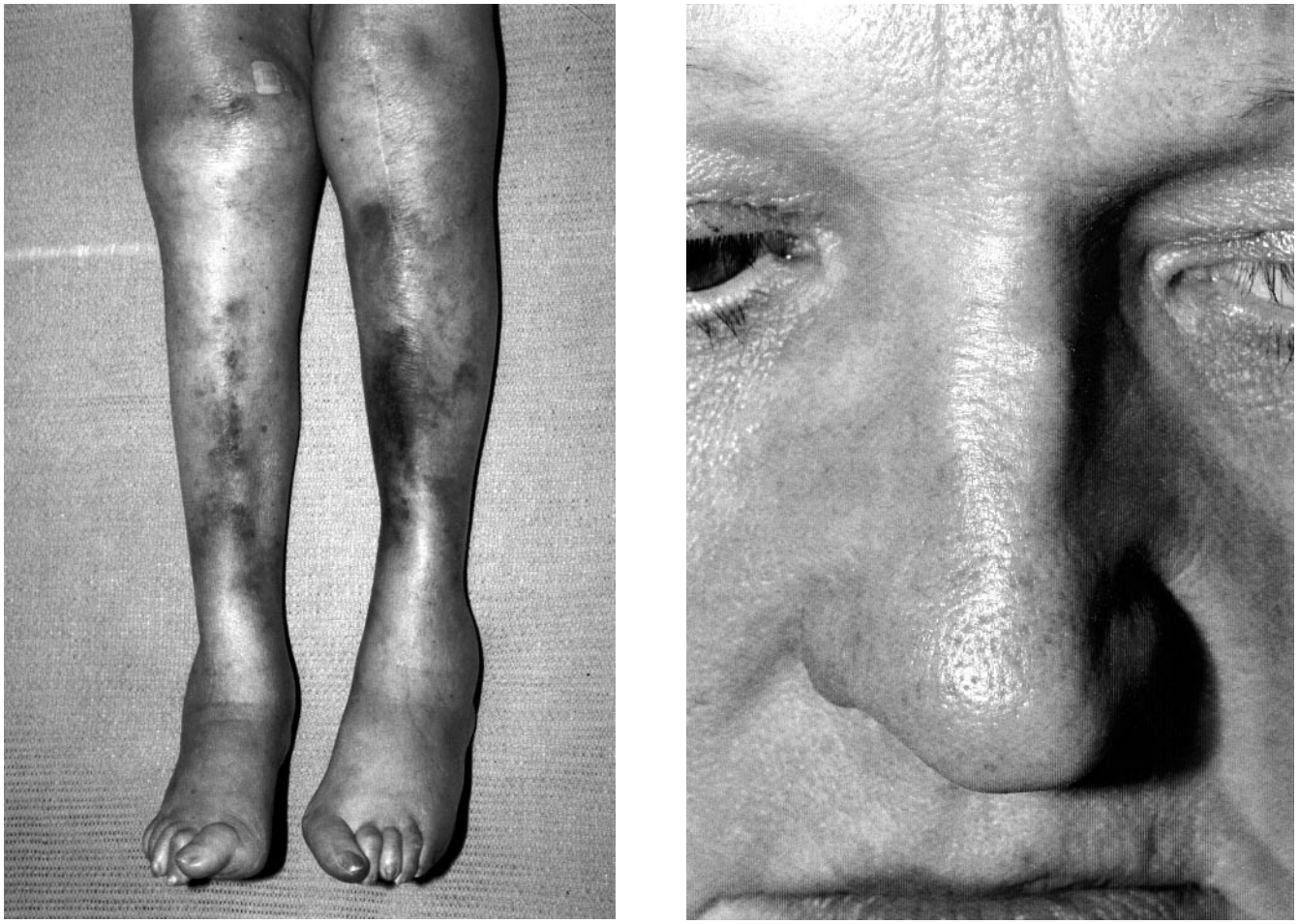

Figure 1. Examples of minocycline pigmentation in our population. A. Type II pigmentation on the legs (Patient 7). B. Type I pigmentation on the face, 2 years after stopping minocycline (Patient 1).

A slightly higher proportion of patients in the pigmentation group were receiving prednisolone therapy (18% vs 12.5%), but small numbers preclude drawing firm conclusions.

Our study excluded patients who had taken therapy for less than 3 months as initial consultations illustrated that this group was less likely to remember details of therapy. Many had taken it only a few days or weeks and so were less likely to have developed hyperpigmentation; however, it is possible that we may have missed some patients with type II pigmentation.

The information obtained for study was predominately from telephone consultations between the patients and one author (GR), with some information derived from patients' case records and face-to-face consultation. This is a potential weakness of our study, as it relied on descriptions of pigmentation being given to the patients without direct examination of pigmentation in some cases. Assuming that the 9 patients who were examined specifically for this purpose are representative of the whole group, it is more likely that pigmentation was underestimated. It has become apparent that arm and leg pigmentation were often attributed to other causes, e.g., venepuncture. The retrospective design of this study meant it was not possible to document precisely when pigmentation developed in each patient. We relied mainly on the patient's recollection, since the onset of pigmentation is gradual and hence most frequently develops between clinic visits. The majority of patients did not seek medical assistance in the early stages (and some not at all). Tendency to burn in the sun did not appear to be a risk factor for the development of pigmentation.

It is important that patients are informed of the risk of pigmentation prior to starting therapy, as pigmentation on exposed areas can cause considerable distress. In our experience, however, most patients are prepared to accept the risk in favor of an efficacious DMARD with minimal side effects, particularly if other DMARD have failed or resulted in significant toxicity. A prospective study with clearly defined endpoints would help clarify information for patients considering this treatment.

An accurate description of the types of pigmentation should be provided to primary care physicians, since lack of awareness and misdiagnosis can cause further distress to patients.

Although minocycline induced hyperpigmentation is common in RA, affecting 41% of patients in our group, it is well tolerated by most patients. Patients and general practitioners should be provided with adequate information about minocycline induced pigmentation at the outset of therapy.

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