weekly and Femodene [1] standard strength combined oral contraceptive (gestodene 75 μg + ethinylestradiol 30 μg) (combined oral contraceptive).

Her arthritis improved with the methotrexate but she developed intermenstrual bleeding of bright red blood for 3 h after every methotrexate dose. She stopped the methotrexate for 2 weeks and bled again after rechallenge. Her normal withdrawal periods became heavy whilst taking methotrexate and were associated with right iliac fossa pain.

She stopped taking methotrexate after 3 months and her intermenstrual bleeding also stopped.

Menstrual irregularities have been reported in association with methotrexate [2–4] but they are uncommon and not often considered in routine clinical practice. To our knowledge, this is the first case report on methotrexate associated with breakthrough uterine bleeding in a patient taking the combined contraceptive pill. As effective contraception is vital to the management of young female patients taking methotrexate [2–4], we feel this case warrants further discussion.

Methotrexate may interact with the oestrogen and progesterone components of the combined oral contraceptive pill at a number of sites. Methotrexate is extensively protein-bound [2] and is renally excreted unchanged, with a half-life of approximately 7 h in low-dose treatment [5]. Circulating oestrogens and progestogens are largely protein-bound [6, 8]. In addition, oestrogen causes an increase in proteins, particularly globulins, that bind hydrocortisone, thyroxine and iron. As a result the total plasma concentration of bound substances is increased, though the concentration of free and active substance remains normal [6].

Since oestrogens are partially metabolized by cytochrome P450 3A4 (CYP3A4), inducers or inhibitors of CYP3A4 may affect oestrogen metabolism [8]. Well-known CYP3A4 inducers include St John’s wort preparations, phenobarbital, carbamazepine and rifampicin. These may reduce the plasma concentration of oestrogens, resulting in a decrease in therapeutic affect and a change in the uterine bleeding profile. CYP3A4 inhibitors include erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice and they may increase oestrogen plasma concentrations and its side effects [7, 8].

There is no evidence that methotrexate causes (i) enzyme induction or (ii) impairment of the efficacy of or (iii) interference with the metabolism of oral contraceptive steroids.

In our patient, it is difficult to postulate the cause of breakthrough bleeding. The timing in relation to her methotrexate suggests a rapid effect, either a direct effect of methotrexate on the uterus or possibly by displacement of oestrogen or progesterone from protein binding sites. The fact that this patient was 4 months post-partum may have lowered her threshold for vaginal bleeding, but the implication was that her combined oral contraceptive is not entirely effective. Contraception at this stage of the patient’s life was vital. As the patient was methotrexate-naive, this could also have been an idiosyncratic effect in this individual patient.

Similar cases may be unrecognized, as contraceptive and menstrual histories are not routinely taken during rheumatology outpatient consultations.

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L. WILLIAMSON, K. YEIN

Rheumatology Department, Great Western Hospital, Swindon and Marlborough NHS Trust, Swindon SN3 6BB, UK

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Correspondence to: K. Yein.
E-mail: khin.yein@smnhst.swest.nhs.uk


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Extremely high titer of anti-human chimeric antibody following re-treatment with rituximab in a patient with active systemic lupus erythematosus

Sir, In a recent issue and elsewhere [1, 2] we reported five cases of life-threatening refractory systemic lupus erythematosus (SLE). In May 2004, one of the patients had a flare-up after 18 months’ remission and infusion of rituximab was employed again. However, it did not reduce disease activity because of the development of anti-human chimeric antibody (HACA) against rituximab. There is growing evidence for the efficacy of rituximab in refractory SLE [1–5]. However, prevention of production of HACA could become important for successful treatment of SLE with rituximab. Little is known about HACA in SLE at present.

We present our case in detail and also describe the characteristic features associated with the development of HACA in autoimmune disease.

A 35-yr-old woman was diagnosed with SLE in 1991 and had been treated since then with repeated steroid pulses, intravenous cyclophosphamide infusion and cyclosporin A. However, her level of consciousness deteriorated to stupor because of involvement of the central nervous system (CNS), with an extremely high titer of anti-dsDNA antibody in June 2002 despite intensive conventional therapies. Finally, a decision was made to treat the patient with the anti-CD20 monoclonal antibody rituximab, which is known to be highly effective against B-cell depletion, based on the consideration that the serious status of CNS lupus was mainly due to autoantibodies from activated B lymphocytes. Just 2-weekly infusions of rituximab (375/m² of body surface area) resulted in dramatic recovery from her catastrophic status, and the patient became fully alert with significant improvement of proteinuria being noted at day 30. In addition, anti-dsDNA antibody and complement levels returned to normal at day 90. It is noteworthy that the above improvement of clinical signs, symptoms and laboratory findings remained normal and the SLEDAI (SLE disease activity index) was less than 2 points even after tapering of betamethasone. The above treatment allowed the patient to go back to her job within 6 months of her life-threatening status.
Fig. 1. Clinical course and response to treatment with rituximab. Rituximab was administrated at 375 mg/m^2 body surface area twice weekly at the indicated hatched arrows, together with 1 mg of betamethasone. Top graph: anti-dsDNA antibody (open circles) and human anti-chimeric antibody (HACA; closed circles) examined by enzyme-linked immunosorbent assay. Bottom graph: expression of CD19 (open circles) and CD20 (closed circles) on peripheral lymphocytes as determined by flow cytometric assay.

After about an 18-month remission, SLE flare-up occurred in July 2004 with a rise in anti-dsDNA antibody titer, hypocomplementemia, lymphocytopenia and high positivity of CD19 cells (21.7% of white blood cells) and CD20 (25.4%). After the infusion of rituximab, almost all CD20 molecules on B cells are consistently saturated with rituximab without any internalization. Therefore we also observed CD19, which is also exclusively expressed on B cells, to evaluate the depletion of B cells. Although 2-weekly infusion of 375 mg/m^2 of body surface area of rituximab was administered, it did not resolve disease activity and anti-dsDNA antibody progressively increased to 1244 IU/ml as shown in Fig. 1. The severity of proteinuria worsened to 2 g/day and more than 4% CD19-positive lymphocytes were still noted after rituximab infusion, while CD20-positive cells were detected only 10 days after the second infusion of rituximab. We considered the possible development of HACA against rituximab and examined the blood concentration of rituximab and HACA. The blood concentration of rituximab was lower than the detectable level (0.1 μg/ml) on 21, 28 and 35 days after initial infusion as well as just before the rituximab infusions. Furthermore, an extremely high titre of HACA against rituximab was detected even just after rituximab infusion.

Rituximab is a genetically engineered chimeric murine variable regions/human IgG1 anti-CD20 monoclonal antibody [6]. Recent studies have shown that rituximab is effective for SLE as well as haematological malignancies [1–5]. Regarding the mechanism of action of rituximab in SLE, we provided evidence that rituximab not only reduces B-cell numbers by in vivo deletion but down-regulates co-stimulatory molecules on B cells, resulting in disturbed T-cell activation [1]. Reduction in both the quantity and quality of B cells suggests that rituximab could improve the disease course in patients with refractory SLE.

Recent studies have reported detection of an autoantibody against rituximab following such treatment [5], and that the detection rate was significantly higher in SLE than in lymphoma patients [5, 7]. Specifically, high-titre HACAs were detected in six of 17 SLE patients [5] but in only one of 166 lymphoma patients [7]. These results suggest that human–mouse chimeric antibodies may be more immunogenic in autoimmune disease, especially in SLE, because of the highly activated B-lymphocyte status.

High titres of HACA in SLE were reported to be associated with disease activity, reduced B-cell depletion, low levels of rituximab and loss of efficacy of rituximab at 2 months after the initial infusion [5]. With regard to the present case, although HACA was not detected just before rituximab infusion, the titre at 3 weeks after the first infusion was one order higher than that reported in a previous paper [5]. Furthermore, serum rituximab could not be detected even at 14 days after the second infusion. These findings suggest prompt development of HACA on the background of extremely high disease activity (SLEDAI = 21 points), resulting in neutralization of rituximab and abolition of the therapeutic effect of rituximab in our patient.

The issue of drug-related antigenicity is not unique to rituximab. In a 26-week phase II study of infliximab, which is also a mouse–human chimeric antibody used to block tumour necrosis factor-α, 21% of rheumatoid arthritis patients treated with standard-dose infliximab (3 mg/kg) developed infliximab-specific HACA. Concomitant therapy with low-dose weekly methotrexate significantly diminished the incidence of HACA [8]. In a more recent cohort study of patients with Crohn’s disease treated with serial infusions of infliximab, concomitant immunosuppressive therapy led to a lower incidence of HACA and a more prolonged duration of response. Pre-medication with intravenous hydrocortisone significantly reduced HACA levels but did not eliminate HACA production or infusion reactions [9]. In this regard, Sandborn [10] proposed that one optimization strategy is the use of immunosuppressive therapy for a clinically relevant period of time with azathioprine for 2–3 months or methotrexate for 1.5–2 months prior to initiating infliximab. However, our patient was also on azathioprine prior to the infusion of rituximab to prevent
HACA production, but it resulted in severe granulocytopenia, necessitating discontinuation of the medication. However, rituximab maintenance therapy is also reported to successfully control SLE. In one such study, two patients were treated with rituximab (375 mg/m² x 4, repeated at weekly intervals) followed by maintenance therapy with rituximab 375 mg/m² every 3 months. At 30 months after the commencement of rituximab therapy, both patients were free of symptoms [4]. Thus, repeated treatment with rituximab seems to induce persistent suppression of B-cell function and reduce the likelihood of development of HACA.

In conclusion, SLE is a representative autoimmune disease characterized by polyclonal activation of B lymphocytes and production of diverse autoantibodies. The frequency of HACA production among SLE patients appears to be high compared with patients with haematological malignancies or other autoimmune diseases. Since the development of HACA results in the negation of a strong weapon against refractory SLE, we must pay attention to the possible development of HACA, especially in the case of re-treatment with rituximab. Concomitant treatment with immunosuppressants or repeated maintenance therapy seems to be a useful strategy to prevent production of HACA. We have to establish a practical strategy to prevent the development of HACA in SLE.

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K. Saito, M. Nawata, S. Iwata, M. Tokunaga, Y. Tanaka
The First Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine, 1–1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan
Accepted 14 July 2005

Correspondence to: Y. Tanaka, The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, 1–1 Iseigaoka, Yahatanishi, Kitakyushu 807-8555, Japan. E-mail: tanaka@med.uoeh-u.ac.jp


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Re: Style versus substance in artistic depiction

Sir, Appelboom [1] suggests artistic rendition of rheumatoid arthritis by Rubens, predicated upon identification of swan-neck deformity and metacarpophalangeal and proximal interphalangeal joint swelling. While I did not recognize a swan’s neck deformity in The Three Graces, the proximal and distal interphalangeal joint swelling in The Miracle of St Ignatius of Loyola is impressive. The prominent nodular appearance of those interphalangeal joints seems, however, more in keeping with a diagnosis of severe osteoarthritis of the hands. I was unable to determine whether apparent slight metacarpophalangeal joint swelling might simply be a visual artefact related to positioning of the hand.

The real challenge, however, is distinguishing substance and style [2, 3]. Do the renditions of Rubens accurately depict disease phenomena (as Appelboom suggested for The Three Graces in 1987) [4] or are they simply stylistic, as suggested by Louie’s analysis of the work of Renoir [3]? The conference that Appelboom chaired in 1987 provided great insights to the difficulties of distinguishing style and substance and did much to advance perspectives of this problem [4].

Leonardo da Vinci is perhaps considered one of the most accurate illustrators of his time. His depictions of an in situ fetus in RL19101r, K/P 197v from the Royal Collection (also known as ‘Illuminismo’) provides important insight [5]. The apparent metacarpophalangeal joint and irregular finger swelling must be stylistic, as actual fetal disease of this nature is unknown. If some of Leonardo’s renditions are stylistic, how can the work of other artists be confidently attributed? As Appelboom noted, confident historical documentation is obtained from examination of the skeleton [1]. Such analysis documented rheumatoid arthritis as a North American disease with only relatively late penetration into Europe [6, 7]. Appelboom’s appropriate placement of a question mark at the end of the title of his article [1] highlights his attention to the style–substance question.

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B. Rothschild
Northeastern Ohio Universities College of Medicine, 5500 Market, Youngstown, OH 44512, USA
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Correspondence to: bmr@neoucom.edu