Leflunomide is now approved for the treatment of rheumatoid arthritis (RA) and has a good safety profile. Common adverse events reported during drug trials included gastrointestinal symptoms, reversible alopecia, transient alterations in liver function tests, and hypertension. Unusual side effects have been recently reported with transient alterations in liver function tests, and hypertension included gastrointestinal symptoms, reversible alopecia, of its mode of action. Demonstrated the involvement of the drug, allowing a study also a positive dose-response effect. A reintroduction further administration, showing not only a temporal relationship but of lupus erythematosus after leflunomide were negative, C3 and C4 levels were normal, and anti-ENA antibodies (anti-SSA and anti-SSB) were positive. A skin biopsy showed features of discoid lupus erythematosus (fig 1C). Leflunomide was discontinued, the skin rash completely resolved within 4 weeks and the antinuclear titre decreased to 1/640. There were no other clinical or biological lupus manifestations—in particular, no nephropathy.

During the following 2 years, the patient was treated with azathioprine, cyclophosphamide, and infliximab combined with methotrexate, but these drugs had to be discontinued because of lack of efficacy or poor tolerance. After pressure from the patient who considered leflunomide to be the most active drug for her arthritis symptoms, this treatment was reintroduced in January 2003 at a low dose of 10 mg daily. Three months later, she was free of skin lesions but noted no improvement in her arthritis. With her consent, leflunomide was increased to 20 mg. When seen 3 months later in July 2003, she presented an acute lupus-like skin rash over the face, neck and arms (fig 1A) that had appeared 8 days after the increase to 20 mg. Moreover, she now had leucopenia, increased titre of antinuclear antibodies and anti-SSA and anti-SSB antibodies, but antihistone antibodies were negative. A new skin biopsy showed, in addition to epidermal atrophy, a lymphocytic infiltration suggestive of subacute lupus (fig 1D). Immunofluorescence of that skin biopsy showed deposits of IgM and C3 at the dermo-epidermic junction. Again, there were no other signs of lupus. Leflunomide was stopped and the skin rash resolved within four weeks.

One month later, although she was strongly advised not to take the drug, she took again 10 mg a day and quickly developed a severe skin eruption, again typical of subacute lupus (fig 1B). These manifestations disappeared with oral steroids. At this stage, the patient reported that the skin manifestations were identical to those seen at the onset of disease. At that time, she was followed up at the department of dermatology with the diagnosis of cutaneous lupus. However, anti-DNA antibodies were negative and major salivary gland hypertrophy led to bilateral parotidectomy, suggesting that she had Sjögren’s syndrome.

MATERIALS AND METHODS

To explore the systemic immune function, a bioassay based on the induction of interferon γ (IFN-γ) production by interleukin (IL-12) and/or IL18 was carried out with peripheral blood mononuclear cells (PBMC) from this patient, 15 patients with RA, and 14 healthy controls. PBMC from this patient were collected in July 2003, while the patient was active drug for her arthritis symptoms, this treatment was reintroduced in January 2003 at a low dose of 10 mg daily.
7 days. IFNγ was measured by enzyme linked immunosorbent assay (ELISA; DuoSet ELISA Development System human IFNγ, R&D Systems).

RESULTS AND DISCUSSION

This is, to our knowledge, the first case of lupus related to leflunomide. Other autoimmune disorders reported with leflunomide include a few cases of vasculitis and of peripheral neuropathy possibly related to vasculitis.

In this patient the role of leflunomide is based on the following criteria: a temporal relationship seen on two occasions, resolution when the drug was stopped, reappearance of the rash with reintroduction of the drug following a dose-response relationship, and the absence of other candidate drugs. In this case, it should be indicated that the diagnosis was primary Sjögren’s syndrome rather than RA, for which the drug has been registered. Because the patient later described the same rash as at the beginning of her disease, this case is rather a reactivation than an induction of lupus.

The mode of action of leflunomide is not completely known. Its active metabolite A771726 inhibits the mitochondrial enzyme dihydro-orotate dehydrogenase and therefore inhibits the de novo synthesis of pyrimidine in immune cells, particularly in activated T cells. Furthermore, leflunomide inhibits tyrosine kinases and thus suppresses the production of proinflammatory cytokines such as tumour necrosis factor α (TNFα). Suppression of a TNFα-induced cellular response may be one of the mechanisms of leflunomide efficacy in RA. In addition, such a mechanism could explain its contribution to this reactivation of lupus rash. The recent cases of lupus-like syndrome induced by anti-TNF treatment favour such a hypothesis. However, such skin manifestations were not seen when the patient was receiving infliximab combined with methotrexate for four infusions over 3 months. This observation suggests that leflunomide made a direct contribution, in line with the worsening when a higher dose was used.

An effect on the Th1/Th2 balance was evaluated by testing the systemic immune response with a bioassay based on the production of IFNγ by PBMC. In this bioassay, patients with active RA, healthy controls, and our patient (black bar), control patients with RA (n = 15, grey bar), and healthy controls (n = 14, white bar), were stimulated with or without 1 ng/ml IL12 or a combination of IL12 (1 ng/ml) and IL18 (5 ng/ml). IFNγ concentrations in culture supernatants were measured by ELISA.

![Image](https://example.com/image1.png)

**Figure 1** Skin clinical and pathology changes: a typical lupus skin rash seen in July 2003 (A) and in September 2003 (B). Skin biopsy in November 2000 (face) showing signs of discoid lupus (C) and in July 2003 (arm) showing signs of subacute lupus (D).

![Image](https://example.com/image2.png)

**Figure 2** Th1 immune modulation in patients with RA, healthy controls, and our patient. PBMC from the patient (black bar), control patients with RA (n = 15, grey bar), and healthy controls (n = 14, white bar), were stimulated with or without 1 ng/ml IL12 or a combination of IL12 (1 ng/ml) and IL18 (5 ng/ml). IFNγ concentrations in culture supernatants were measured by ELISA.
compared with controls. The picture was thus exactly opposite to that seen in RA.

In RA, the systemic defect of IFNγ production in RA blood compared with controls appears to result from a reduced response to the Th1 inducing cytokines IL12 and IL18. This situation could contribute to the increased incidence of tuberculosis, particularly after TNF inhibition. In this patient, the opposite picture was observed, with an increased response to cytokines inducing Th1. This observation is in line with an effect of leflunomide on the Th1/Th2 balance. In this case, the genetic (B8, DR3) and disease background (primary Sjögren’s syndrome and not RA) may explain the appearance of lupus skin manifestations.

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