Sulphonamide-induced remission in rheumatoid arthritis—a thought-provoking prescribing error

Sir, In 2002, a 50-year-old man with no significant past medical history presented with a 3-month history of pain and swelling of the small joints in the hands. ESR measured 27 mm/first hour and RF was positive. Initial treatment with NSAIDs failed to control his symptoms and after a further 6 months of persistent synovitis, SSZ 1 g twice daily was recommended by the patient’s general practitioner (GP) to treat his RA with arrangements for appropriate counselling and monitoring.

The patient continued to take his prescribed medication and by 2004 was in complete remission, with no pain, participating in regular sporting activity, with ESR recorded at 4 mm/h. He remained under annual review at the rheumatology outpatient clinic, and was viewed as a success story.

In 2009, he registered with a new GP who reviewed his medication. It was identified that he had been taking sulphadiazine 1 g twice daily since the recommendation that he take SSZ, a prescribing error that had occurred at his previous GP practice. His new GP stopped his sulphadiazine immediately and as the patient was in full remission, he continued without disease-modifying therapy until further review by an embarrassed and puzzled rheumatologist.

In 2010, about 9 months after stopping his sulphadiazine, he returned to the rheumatology clinic with mild (but definite) recurrent joint pain and swelling of the small joints of the hands, slightly raised ESR (for him) at 9 mm/h and RF positive. Initial treatment with NSAIDs failed to control his symptoms and after a further 6 months of persistent synovitis, SSZ 1 g twice daily was recommended by the patient’s general practitioner (GP) to treat his RA with arrangements for appropriate counselling and monitoring.

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In 2010, about 9 months after stopping his sulphadiazine, he returned to the rheumatology clinic with mild (but definite) recurrent joint pain and swelling of the small joints of the hands, slightly raised ESR (for him) at 9 mm/h and strongly positive anti-CCP levels. It was tempting to restart sulphadiazine but it was agreed that SSZ be prescribed. Subsequent follow-up in September 2011 found the patient to be in complete remission after restarting the appropriate therapy.

Sulphadiazine is a broad-spectrum, short-acting antibiotic [1]. Indications are limited and include prevention of rheumatic fever recurrence and treatment of toxoplasmosis (unlicensed) [2]. The pharmacodynamic properties are identical to those of other sulphonamide antibiotics, in that it is a competitive agonist of para-aminobenzoic acid preventing bacterial synthesis of folic acid [1]. The intended drug in this case, SSZ, is a combination therapy of sulphapyridine and 5-aminosalicylic acid. The drug itself has anti-bacterial and immunomodulatory properties that have disease-modifying effects in patients with RA.

Studies in vitro have suggested that the SSZ inhibits cytokine release as well as IgM and IgG production [3]. Other in vitro studies demonstrate inhibition of TNF-α in macrophages by induction of apoptosis [4]. Pharmacodynamic studies have revealed various anti-inflammatory properties of the drug or its metabolites such as migration of neutrophils and reduction of proteolytic enzyme production and angiogenesis [5, 6]. Recent research implicates the antioxidant effects of SSZ in reduction of inflammation in RA [7]. It is evident that although the exact mechanism of action of SSZ is unknown, it still provides statistically significant benefits to patients suffering with RA [3].

However, it is still unknown whether SSZ itself or its individual metabolites are responsible for disease modification in RA. This interesting case may indicate that the sulphonamide moiety may play a significant role in the above processes—otherwise the remission induced by sulphadiazine and subsequent relapse following withdrawal of the drug in this patient with RA may have been a remarkable coincidence.

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References


Alterations of skeletal muscle microcirculation detected by blood oxygenation level-dependent MRI in a patient with granulomatosis with polyangiitis

Sr., Granulomatosis with polyangiitis (GPA) is a small vessel vasculitis that is associated with cardiovascular disease, which mainly determines the prognosis of GPA patients [1, 2]. Contradictory evidence has been published regarding accelerated atherosclerosis in GPA, which might cause cardiovascular morbidity [3, 4]. Blood oxygenation level-dependent (BOLD) MRI of skeletal muscle has become a valuable tool for the assessment of vascular pathways such as atherosclerosis, diabetes mellitus and chronic compartment syndrome [5–7]. T2*-weighted MR signal of gradient-echo-echo-planar imaging (EPI) sequences is sensitive to changes of oxyhaemoglobin concentration in small pre- and post-capillary vessels [8].

Here we present a case of a 73-year-old female GPA patient who was treated in our rheumatology clinic owing to severe myalgias. She had a 7-year history of GPA with nasopharyngeal symptoms, haemoptysis, arthritis, dysesthesias and renal involvement. During her actual admission, laboratory tests revealed leucopenia of 2.6/nl (reference range 3.5–10.0/nl), lymphopenia of 0.21/nl (0.9–3.3/nl), haematocrit 0.38/l (0.36–0.46/l), CRP 0.4 mg/l (<10 mg/l), BSG 10 mm/h (0–28 mm/h), ANCA 1:20 (<1:20), anti-MPO <2.5 U/ml (<5 U/ml) and anti-PR3 6 U/ml (<5 U/ml). Her blood pressure was 130/70 mmHg. She had no history of hypertension, diabetes mellitus or hyperlipidaemia. Her peripheral pulse status was normal and she never suffered from claudication. Recent maintenance immunosuppressive medication consisted of 150 mg azathioprine and 10 mg prednisone daily. MRI measurements were indicated owing to severe myalgias of both legs and performed on a 3.0-T scanner (Verio, Siemens Medical Solutions, Erlangen, Germany). Informed consent was obtained, and the study was approved by the local ethics committee (Ethikkommission beider Basel). A T2*-weighted sequence revealed no signs of local inflammatory activity of the calves. For BOLD imaging, a healthy female volunteer controlled for age, BMI and physical activity served as control after providing consent. A multi-echo gradient-echo EPI sequence with fat suppression was used with a cuff compression paradigm as previously described [5, 9, 10]. Briefly, BOLD imaging was performed during the last minute of a 300 s resting period, 180 s of ischaemia and 400 s of reactive hyperaemia. Four axial slices (thickness 5 mm, gap 2.5 mm) were positioned in the upper calf. With each excitation, four echo images with increasing effective echo times were acquired. Inflow (initial signal intensity, I0) and oxygenation (susceptibility, T2*) effects were separated by a pixel-by-pixel least-square fit of a monoexponential decay to the signal intensities at the four different echo times (TE1, 3 of 9.3, 20.1, 31.0 and 41.5 ms) according to $S(I_0, T2^*)=I_0 exp(-TE1/T2^*)$. T2* maps were computed, supplemented with T1-reference images and ROIs placed in the soleus, gastrocnemius and peroneus, excluding pixels of bones and vessels (Fig. 1).

(i) Absolute baseline T2* values were comparable between the two individuals (patient 21.6 ms, control 21.1 ms).

(ii) Absolute and relative minimum ischaemic T2* values (T2*min) were substantially lower in the GPA patient (15.3 ms, −29.4%) than in the control (19.7 ms, −9.5%).

(iii) Relative T2* decline after cuff compression [ischaemic declining slope (IDS)] was significantly steeper in the GPA patient, when compared with the healthy volunteer (−4.1%/ms vs −1.0%/ms).

(iv) Absolute and relative T2* peak values during reactive hyperaemia (T2*max) were strongly reduced in the patient (23.6 ms, +7.0% vs 25.0 ms, +18.4%).

(v) Time to peak value (TPP), reflecting the time from cuff deflation to T2*max, was similar between the two subjects (32 s vs 34 s).

(vi) T2* end value (EV, reflecting medium T2* during the last 10 s of measurement) was higher in the GPA patient compared with the control.

These findings strongly suggest major perturbations of skeletal muscle microcirculation in this GPA patient, revealed by skeletal muscle BOLD MRI. The lower T2*min value in the patient might be explained by increased oxygen consumption as control and patient showed comparable baseline absolute T2* values, and the IDS absolute value was substantially higher in the patient. This might be a compensatory mechanism for chronic hypoxic conditions in patients with GPA. T2*max decrease could be explained by reduced blood flow in skeletal muscle microvessels, owing to small vessel vasculitis. The underlying mechanisms of the detected BOLD alterations have to be interpreted with care owing to other T2* influencing factors such as blood volume, haematocrit, functional vascular status and metabolic changes [5, 7]. Owing to the lack of reference methods for the measurement of perfusion or oxygenation, our findings remain mostly descriptive. However, the measured BOLD response in GPA is different from previous results in patients with atherosclerosis that showed diminished ischaemic T2* decline and a prolonged TPP [5, 10]. This may indicate that other mechanisms besides accelerated atherosclerosis play an important role in the pathogenesis of skeletal muscle microcirculation alterations in GPA. Of course,