Author's response to reviews

Title: Disseminated cutaneous Herpes Simplex Virus-1 in a patient with rheumatoid arthritis receiving Infliximab: A case report.

Authors:

Elizabeth A Justice (elizabethjustice@yahoo.com)
Sophia Y Khan (sophiagoble@btinternet.com)
Sarah Logan (sarah.logan@uhb.nhs.uk)
Paresh Jobanputra (paresh.jobanputra@uhb.nhs.uk)

Version: 4 Date: 9 February 2008

Author's response to reviews: see over
Dear JMCR Editorial team,

**RE: Revised Submission of Manuscript by Justice et al.**

DISSEMINATED CUTANEOUS HERPES SIMPLEX VIRUS-1 IN A PATIENT WITH RHEUMATOID ARTHRITIS RECEIVING INFliximAB: A CASE REPORT

Thank you for your email response dated 16th January 2008 requesting a revised submission of the above manuscript and some very helpful comments from the assigned referees.

Please find attached the revised version of this manuscript. Below is a copy of the referee’s comments (in italics) and our response to each point with changes we have made to the manuscript outlined in red text.

There are no changes to the title, abstract and list of authors. The reference list has changed and now includes 15 references and has been appended to the Case Presentation.

We would like to take this opportunity to thank you for considering the revised version of this manuscript. We very much hope the revisions are to your satisfaction and we hope to hear from you in the near future.

Please do not hesitate to contact me should any queries arise.

Kind Regards,

Dr. Elizabeth Justice
Reviewer 1, Dr Benucci:

1) At the beginning of disease the authors don't reported the dosage of Methotrexate, Sulphasalazyn, Leflunomide and Etanercept, and also the time of therapy for every single drug.

We thank the reviewer for this helpful comment and have expanded the information about drug doses and duration and also reasons for drug withdrawal. This information now makes up the bulk of paragraph 1, page 1 and reads as follows:

Our patient presented in 2004 and was initially treated with methotrexate. She was unable to tolerated doses beyond 15mg per week because of troublesome mouth ulcers. Her disease failed to come under control and she was dependent on oral prednisolone at doses above 20mg. After 5 months she was switched to sulphasalazine 3g daily. She developed severe headaches and 3 months later was switched to leflunomide 20mg daily without any clinical improvement. Her erythrocyte sedimentation rate (ESR) was raised at 44mm/hr despite oral prednisolone at 25mg daily and 10 months after diagnosis was started on Etanercept 25mg subcutaneous injections twice weekly combined with low dose oral methotrexate (10mg/week). 3 months later her ESR had fallen to 26mm/hr and the oral prednisolone reduced to 10mg daily.

2) Also for after switching to Infliximab the authors don't report the Infliximab dose.

Thank you, we have added details of the dose used in paragraph 1, page 1 and reads as follows:

She switched to infliximab, administered intravenously at a dose of 3 mg/kg, and she received the first 3 infusions over the course of 6 weeks.

3) In the discussion the authors don't explain the possible correlation between infection of HSV-1 and the immune state of patient. In particular in every switch therapy don't report the exam such as lymphocyte sub-populations. The role of Infliximab on cytotoxicity antibody-dependent on CD14 cells but also on CD56 that have a role in the host defence to infections. For Adalimumab and the Etanercept the mechanism is different. This problem must be introduced and explained.

Thank you. Measurement of lymphocyte subsets is not routinely done in UK rheumatology practice and no data on this is available for our patient. We have added some detail to the discussion about immune mechanisms but we believe that these remain poorly understood and a detailed emphasis based on various lymphocyte subtypes is beyond the scope of this report.
4) In every switch therapy (from DMARD to biologic blocking agents) wasn't reported the activity of patient in term of DAS28 or ACR and therefore the case worsening was not documented by clinical but also inflammatory parameters ESR and PCR.

We agree with the reviewer that inclusion of inflammatory markers would be useful to the reader and have included ESR data in paragraph 1 of the case presentation. Measurements of DAS scores are not done routinely in our unit on all patients and indeed are of doubtful value in making clinical judgments about switching therapy. We also feel that detailed description of DAS 28 values adds little value to the key points raised by our case.

**Reviewer 2, Dr Ranganathan**

1. on page 6 the description of BSRBR needs to be modified - ....cohort assembled for te study of adverse events ......

We apologise but have been asked to remove the reference to the BSRBR data by Dr. Kimme Hyrich, Clinical Lecturer in Epidemiology in Manchester, for reasons of confidentiality.

2. on page 6, in the same paragraph the authors need to expand on and present a more coherent discussion of the possible mechanisms of TNF and steroids on increased susceptibility to HSV. The three statements provided are disjointed, not coherent and insufficient.

Thank you. We have included more in vivo evidence of the role of TNF-alpha in HSV-1 infections and have re-written the discussion around the effects of steroids on HSV infections. The discussion now reads:

We are not aware of any published reports of serious HSV infections associated with use of TNF inhibitors and cannot say whether treatment with infliximab, steroids alone, or the drug combination caused disseminated HSV-1 in our patient. In vivo data suggests that TNF-alpha may have an anti-viral effect in HSV-1 infections. In a model in which HSV-1 was reactivated in latently infected mice cornea TNF-α and interleukin-6 were the predominant cytokines within the trigeminal ganglion suggesting a key role for these cytokines in viral clearance. Absence of TNF in knockout mice increased susceptibility to primary corneal HSV-1 infections in one study and lowered survival rates compared with wild type mice in another (83% cf 97%). Whilst all three TNF inhibitors used in clinical practice inhibit the actions of TNF-α, their different mechanism of actions may result in a variable susceptibility to HSV-1 infections, although this has not specifically been studied.

In vitro studies of gingival fibroblasts show that cells pre-treated with dexamethasone and infected with HSV-1 gave rise to higher yields of virus suggesting that corticosteroids increase susceptibility to infection in these cells. Recipients of renal transplants on high doses of prednisolone (above 25 mg daily) are reported to have twice the rate of HSV infections compared with those on lower doses including
primary infections in sero-negative patients and re-infections of sero-positive patients. Unfortunately this study does not report the severity and nature of HSV-1 infections seen.

3. one of these statements discusses the rate of HSV in renal transplant patients but it is unclear whether this is localized or disseminated HSV. This needs to be clarified.

The original paper does not Unfortunately expand upon the nature or severity of the HSV infection. It subdivides only into “primary infections in a sero-negative renal transplant recipient” and “reactivation of HSV in a sero-positive recipient”. We take on the reviewer’s concerns and have expanded further the findings of the study whilst highlighting this omission in our discussion. See above for amended paragraph.

4. on page 6, para 3 states that no deaths or irreversible side effects have been reported with acyclovir - serious side effects such as seizures can occur with acyclovir - this para needs to be changed and more complete info on toxicity provided.

Thank you. This has been amended to include rare serious side effects of acyclovir and reads as follows: whilst oral acyclovir has a good safety profile, cases of rapidly progressive acute neurological and renal toxicity have been described. Acyclovir-induced neurotoxicity can present with a variety of symptoms including agitation, delirium and hallucinations.

5. In the same para, any data on duration of acyclovir therapy for secondary prevention of HSV should be discussed. The authors decision to continue the patient on 200mg alternate day of acyclovir appears arbitrary and any literature to support this if available should be cited.

We fully accept that the decision to continue on 200 mg alternate days is arbitrary and not evidence based. However the evidence, as indicated in our report, is limited and our decision to continue at this dose was in discussion with the patient. We have clarified this point in the discussion with the statement: whilst the current evidence around the optimum duration and dose for long-term prophylaxis is lacking, a decision to continue on this low level of therapy was taken with the patient because of concerns about infection recurrence.

6. Although the report discusses both HSV and pustular psoriasis as side effects of anti-TNF therapy, the discussion is skewed with more emphasis and detail on HSV and only a brief mention towards the end of psoriasis. The discussion on psoriasis needs to be expanded with emphasis on possible mechanisms of this unusual adverse event in patients on anti-TNF therapy.

We have deliberately skewed the focus of our discussion towards the HSV aspect as cases of psoriasis have been extensively described elsewhere. We have added a
paragraph in the discussion about the postulated mechanisms of the development of psoriasis in anti-TNF therapy. This reads:
There is no clear explanation as to the nature of this phenomenon. Sfiakis postulates that under certain conditions TNF-α inhibition promotes the activation of autoreactive T cells leading to tissue damage via autoimmune pathways\textsuperscript{15} whilst De Gannes speculates that increased expression of interferon-α in the dermal vasculature may increase susceptibility to psoriatic skin lesions \textsuperscript{14}.