usefulness of the NF-κB reporter assay with mutant NOD2 for observing its role in EOS/BS, although the MAP kinase activation pathway and other possible pathways need to be evaluated to more completely understand the pathogenesis of the NOD2 mutation in EOS/BS.

We have identified the first deletion mutation in the NOD2 gene responsible for EOS/BS, and the mutant showed constitutive activation of NF-κB, which is one of the key features that lead to the pathogenesis of EOS/BS.

### Rheumatology key message

- A six-base deletion in NOD2 gene causes EOS.

### Acknowledgement

This work was carried out at Department of Pediatrics, Kyoto University Graduate School of Medicine, Kyoto, Japan.

**Funding:** This work was supported by grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology and grants from the Japanese Ministry of Health, Labor and Welfare.

**Disclosure statement:** The authors have declared no conflicts of interest.

### References

9. Hidemasa Sakai1, Shusaku Ito2, Ryuta Nishikomori1, Yuuki Takaoka1, Tomoki Kawai1, Megumu Saito1, Ikuo Okafuji3, Takahiro Yasumi1, Toshio Heike1 and Tatsutoshi Nakahata1

1. Department of Pediatrics, Kyoto University Graduate School of Medicine, Kyoto, 2. Department of Dermatology, Hitachi General Hospital, Hitachi and 3. Department of Pediatrics, Kobe City Medical Center General Hospital, Kobe, Japan

Accepted 27 August 2009

Correspondence to: Ryuta Nishikomori, Department of Pediatrics, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: nishiko@kuhp.kyoto-u.ac.jp

**Comment on: Hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with methotrexate**

Sir, We read with interest the recent article by Amital et al. [1] that compared hepatotoxicity rates in PsA and RA patients treated with MTX based on the evaluation of standard liver function tests. The authors conclude that the incidence of hepatotoxicity does not differ between the two disease groups after adjusting for the cumulative dose of MTX.

Several studies in MTX-treated psoriasis patients have reported that isolated abnormalities of liver enzymes (i.e. alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase) were poor predictors of the severity of liver histopathology. The authors state that the combined sensitivity of aspartate aminotransferase, alanine aminotransferase and bilirubin for detecting an abnormal liver biopsy has been rated at 0.86 based on a previous study [2]. This figure implies that 14% of those with normal liver function tests will have undetected hepatic disease. Larger studies have suggested that 30–50% of the psoriasis patients on MTX have normal standard liver function test results despite histology showing fibrosis and cirrhosis [3]. The lack of correlation between liver enzymes and hepatic fibrosis and cirrhosis has been the major factor leading to the recommendation that liver biopsies be done to monitor potential hepatotoxicity. In this study, the liver function tests were performed with varying frequency which could allow abnormal liver function tests to be missed. The authors acknowledge that the rates of other hepatotoxic agents such as alcohol use and the occurrence of other hepatic comorbidities were not known. We believe that these are significant confounding variables, which make the interpretation of the results of this study difficult. The British Association of Dermatologists recommends serial monitoring...
of procollagen III peptide as a marker of hepatotoxicity in MTX-treated psoriasis patients [4]. The US psoriasis task force guidelines advise liver biopsy for those with persistent liver function test abnormalities during treatment or after 3.5–4g total cumulative dose of MTX in low-risk patients [5]. It is our opinion that standard liver function tests alone are insufficient in monitoring for potential hepatotoxicity in psoriasis patients on MTX. We believe that given potential confounding variables between the groups, the statement that ‘hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with MTX’ is premature.

Disclosure statement: The authors have declared no conflicts of interest.

Maeve Lynch1 and Brian Kirby1
1Department of Dermatology, St Vincents University Hospital, Dublin, Ireland
Accepted 14 September 2009
Correspondence to: Maeve Lynch, Department of Dermatology, St Vincents University Hospital, Elm Park, Dublin 4, Ireland. E-mail: lynchmaeve@yahoo.ie

References

Rheumatology 2010;49:197–198
doi:10.1093/rheumatology/kep323
Advance Access publication 14 October 2009

Comment on: Hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with methotrexate: reply

Sir, We thank our colleague for the well-written and interesting comments [1] regarding our study [2]. The differences between the views of dermatologists and rheumatologists regarding prevention of MTX hepatotoxicity are well known; policies and approaches differ between these two medical communities. We believe that the major drawback of the current attitudes and guidelines held by many dermatologists are that they are not based on satisfactory evidence.

The current recommendations are based on studies, some quoted by Dr Lynch, which were conducted in psoriatic patients more than two decades ago; however, these studies encompassed a limited number of patients. In the study by O’Connor et al. [3] that was also mentioned in Dr Lynch’s comment, liver enzyme monitoring was shown to be a good predictive model for positive findings from liver biopsy specimens of psoriatic patients; however, this model was based on only 78 patients, so far no consensus has been reached on the predictive value of liver function tests regarding liver histology in psoriasis patients.

Our study has weaknesses; as we mentioned, clinical data were retrieved from the electronic files of all psoriatic and rheumatoid patients treated by the Maccabi health maintenance organization that insures more than 1.7 million members in Israel. However, some parameters that we wanted to analyse, such as consumption of alcoholic beverages, other hepatic comorbidities and liver biopsy results, were not coded and therefore not available for analysis. Although a possible confounder, one should know that consumption of alcoholic beverages and the rate of alcoholism in Israel is extremely low compared with European countries; therefore, this parameter probably had no major impact. Furthermore, we believe that these non-differential misclassification biases are unrelated to disease type and status and, therefore, are not potential confounders.

Interestingly, although our data showed that rheumatoid patients had higher rates of abnormal liver enzymes than did psoriatic patients, this statistic did not reach significance. Our study has significant strengths. The computerized data enabled access to a ‘real-life population’ of several hundred patients who were managed routinely. Given the potential hazards of liver biopsies, we believe that the current recommendations should be revisited.

Disclosure statement: The authors have declared no conflicts of interest.

Howard Amital1, Yoav Arnson1, Gabriel Chodick2 and Varda Shalev2
1Department of Medicine ‘D’, Meir Medical Center, Kfar-Saba and 2Department of Medical Informatics, Maccabi Healthcare Services, Israel
Accepted 3 September 2009
Correspondence to: Howard Amital, Department of Medicine ‘D’, Meir Medical Center, Kfar-Saba, Israel.
E-mail: howard.amital@clalit.org.il

References