Differential expression of interleukin-6 in leprosy reactions

Sir,

We read with interest the publication of Moreno *et al*.[1], where interleukin-6 levels in serum of leprosy patients with erythema nodosum leprosum were compared with the patients having untreated multibacillary leprosy without erythema nodosum leprosum and healthy individuals. The study concluded that high serum levels of interleukin-6 were observed in erythema nodosum leprosum, predominantly in patients having severe reactions.

Over the course of the disease, leprosy patients may get complications, such as an acute hypersensitivity response against *Mycobacterium leprae* antigens, resulting from immune response. The leading complications of leprosy are type 1 and type 2 reactions, the latter also known as erythema nodosum leprosum. These distinct disorders appear independently but can emerge at varying occasions in the same patient. It is necessary to acknowledge that any of these conditions can lead to irreversible nerve damage. Erythema nodosum leprosum is common in leprosy patients who have a high bacterial load and a low- to- no immunity, specifically in lepromatous and borderline lepromatous cases of leprosy.[2]

Interleukin-6 was one of the first identified cytokines which has been widely recognized as a biomarker in several mycobacterial diseases including leprosy.[3,4] However, as clearly stated in the article by Monero *et al*.[1]: 'Studies evaluating serum levels of interleukin-6 in erythema nodosum leprosum have shown discordant results.' Many studies reported that differential expression levels of interleukin-6 are associated with both type 1 and type 2 reactions when compared with individuals affected with leprosy without any reaction. This is an intriguing finding and should be considered for future studies.

The authors checked the levels of interleukin-6 at M0 (beginning of leprosy reactions) and M1 (one month later), and then compared with untreated leprosy patients without type 2 reaction or erythema nodosum leprosum (designated as controls) to conclude that interleukin-6 was elevated only in ENL (M0). However, analysis of interleukin-6 levels in the patients having type 1 reaction should also have been taken into consideration. In our opinion, in such kind of studies, it would be interesting to know the trend of the expression of interleukin-6 or any other predictive biomarker in both type 1 and type 2 reactions in a cohort study. An example of this approach is the study of Sousa *et al*., where the objective was to assess the role of interleukin-6 and its variants in type 1 and type 2 reactions. The study included the samples from both type 1 and type 2 reactions which gave an unbiased result of an interleukin-6 variant associated with type 2 reaction which suggested that interleukin-6 may become a potential biomarker for type 2 reaction leprosy phenotype.[5] Similarly, to get a proper idea of the identification of individual biomarker in a certain condition, any subsequent work should use both the reactions during the experiments to get a clear idea as to which reaction type has the highest expression in the serum level of interleukin-6 along with the other possible prospective biomarkers, as done by Saini *et al*. and others in their study.[6] Using interleukin-6 expression as a 'negative control' for type 1 reaction may be useful in proving such a hypothesis, where any change of titre would not be expected due to any variable used in the experiments.

To conclude, we would like to congratulate Moreno *et al*. for their valuable work. The work is a step closer to recognising the role of interleukin-6 in leprosy type 2 reactions as a prognostic biomarker. We further hope that through this paper, relevant information will be disseminated regarding the usage of baseline for sample type in the experimental design to explore further the debatable role of interleukin-6 during lepra reactions.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Authors' reply

Sir,

We thank the authors of the letter[1] for their interesting comments on our article.[2]

We developed this study to evaluate serum levels of some mediators involved in the innate and adaptative immune response of leprosy patients with erythema nodosum leprosum, since this reaction leads to severe peripheral nerve damage and physical incapacity as well as pain and malaise that deprive patients from social and economic interactions. Thus, the identification of possible serum immunomarkers for erythema nodosum leprosum could open new strategies for treatment and prevention, avoiding or reducing the nerve damage that impairs severely the quality of life of leprosy patients.

In our study, of special interest was the observation of the high serum levels of interleukin 6 (IL-6) at M0 (at the beginning of reaction) compared with M1 (one month later) and with untreated multibacillary leprosy patients without erythema nodosum leprosum (control with leprosy: CTRL), similar to the studies reported in the literature.[3-7] In addition, we observed higher serum levels of IL-6 in patients with severe erythema nodosum leprosum than in those with moderate or mild reaction. Considering that the IL-6 levels decreased after the remission of the reaction of erythema nodosum leprosum, we suggest that this cytokine has a role in erythema nodosum leprosum episodes and could be used as a marker for erythema nodosum leprosum in multibacillary leprosy patients.

We agree with the authors regarding the importance of evaluating the serum levels of IL-6 in patients with type I reaction together with erythema nodosum leprosum patients, as realised by Sousa *et al*.[6] and Saini *et al*.[8] In fact, we emphasise that our intention in our study was to evaluate and to follow-up erythema nodosum leprosum patients for two years after the initial erythema nodosum leprosum reaction. In this regard, the follow-up of 13 erythema nodosum leprosum patients showed that 11 had new episodes of erythema nodosum leprosum, reinforcing the importance of identifying biomarkers that may indicate early development of reaction.

Another important point to consider is the use of IL-6 as prognostic marker to erythema nodosum leprosum. For this purpose, it is necessary to follow the levels of this cytokine in a cohort of multibacillary leprosy patients and observe if patients that develop erythema nodosum leprosum present an increased level of IL-6 before the reaction. If a prognostic role of IL-6 is confirmed, it will enable us to take early prophylactic or therapeutics measures to prevent or minimise the damage due to the reaction.

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