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EDITORIAL

Infliximab in extrapulmonary sarcoidosis: tantalising but inconclusive

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It is a truth universally acknowledged that a new therapy with exciting prospects must be in want of placebo-controlled evaluation. In this issue of the *European Respiratory Journal*, JUDSON *et al.* [1] report that in a study of patients with sarcoidosis, the combined group with one of two infliximab regimens had a statistically significant reduction in the degree of extrapulmonary organ involvement, compared with the placebo group. Infliximab has been reported to be beneficial in small groups of patients with aggressive sarcoidosis and, therefore, it might be thought that the data of JUDSON *et al.* [1] herald a brave new therapeutic future for infliximab in extrapulmonary disease. The reality is otherwise. The data provide limited encouragement for the use of this therapy in extrapulmonary sarcoidosis, but the findings are, simply put, inconclusive. There appears to be an almost equal likelihood of an overstatement and an understatement of a treatment effect, for two different reasons.

The bias inherent in placebo-controlled evaluations of novel therapies now requires urgent attention. In brief, if a novel studied treatment is also available for open use, patients and referring physicians may be less likely to accept its enrolment in a placebo-controlled study [2]. Trials of therapies that are not routinely available are quite another matter. In the study by JUDSON *et al.* [1], the primary purpose was to measure efficacy in pulmonary disease but the *post hoc* analysis of a systemic therapeutic effect creates its own difficulties. More importantly, it is known that open infliximab therapy was available, to some of these investigators, for patients with more aggressive disease and it can reasonably be argued that the enrolled population was a relatively nonprogressive subgroup with, by definition, less opportunity for a treatment benefit. This concern applies equally to the small, average therapeutic benefit for a forced vital capacity (FVC) of <5% in the primary study in pulmonary sarcoidosis [3], and to recent trials of oral and intravenous cyclophosphamide in systemic sclerosis with similarly ''disappointing'' FVC effects [4, 5]. Thus, selection bias may seriously distort the quantification of a treatment effect.

In principle, this issue should be confronted vigorously in discussion by the authors of therapeutic trials who have, after all, the deepest insight into the nature of their studied populations. However, no author of a pharmaceutical study is comfortable voicing the thought that a treatment effect might be understated. A hardy scepticism is generally thought to be the correct ''scientific'' response; treatment effects in therapeutic studies are, it seems, always considered to be overstated. In the study of JUDSON *et al.* [1], the problem of placebo-controlled bias makes a cameo appearance in the discussion section but the authors rapidly reach the conclusion that speculation on this particular question ''remains conjectural''.

Perhaps this is so, but there is strong circumstantial support for marked selection bias in another recent study in which open therapy was also routinely available. Strikingly, in a placebo-controlled study of oral cyclophosphamide in systemic sclerosis, only 15% of patients were considered by their physicians to require open therapy at the end of the study [6]. Placebo-controlled evaluation is widely viewed as the best possible study design but sometimes ''the best is the enemy of the good''. Definitive studies of treatments used to slow progression can, by definition, provide only small benefits in the subset of patients with indolent disease. In diffuse lung disease, there is a very real risk that potentially effective treatments might be undermined by meaningless mean statements of treatment effects in biased populations, simply because placebo-controlled evaluation does not capture clinical reality. In systemic sclerosis, the scleroderma lung study group based power calculations on the expectation of a much larger treatment effect from cyclophosphamide, drawing upon open-treatment data. However, open treatment with potentially toxic and unproven therapies tends to be reserved for patients with disease that concerns clinicians, with a greater scope for a striking treatment benefit. Earnest attempts to quantify the ''clinical significance'' of an average effect on pulmonary function indices, or in the study by JUDSON *et al.* [1], on systemic involvement, effectively miss the point. The true amplitude of a treatment effect is likely to lie somewhere between placebo-controlled and open observations.

Where, then, does this leave clinicians who wish to apply the data of JUDSON *et al.* [1] in practice? The difficulties do not end with the problem of population bias because this study has other methodological limitations, as might be expected when *post hoc* analyses are linked only loosely to the primary purpose of a study. New treatments should be evaluated with established primary end-points. Novel end-points should be validated in a less rarified atmosphere, ideally in the setting of standard therapy, in which observed change can be compared

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with that expected from traditional methods of serial evaluation. However, in the current study, a treatment of uncertain efficacy has been assessed using the extrapulmonary Physician Organ Severity Tool (ePOST), an end-point of undetermined accuracy. The ePOST system, if ''system'' is the correct term, amounts to the simple addition of organ involvement scores. It should be acknowledged that there was little choice but to construct a single score that was amenable to analysis. JUDSON *et al.* [1] argue cogently that other systems used to quantify systemic disease [7, 8] could not be applied in this retrospective analysis of a database established primarily for other purposes. The necessary information was lacking. In essence, it was necessary to construct a new approach, largely without guidance from previous observations. This *modus operandi*, famously described in aviation circles as ''flying by the seat of one's pants'', is certain to be unsatisfactory at one level or another.

The applicability of data to pragmatic decision-making ranks high in the hierarchy of things that matter to clinicians. It is traditional for those who write textbook chapters to construct long lists of indications for treatment of sarcoidosis but, in reality, there are two broad reasons to introduce or change treatment: danger, of death or damage to major organs; and unacceptable impairment in quality of life. These distinctions are blurred in some patients and coexist in others. Nonetheless, this essential dichotomy informs the whole doctor–patient relationship. The judgement that treatment is required for dangerous disease should be based on accumulated medical experience, and the role of the physician is to provide robust advice. In contrast, patients are their own experts when it comes to estimating their quality of life and they should, ideally, be encouraged to make an informed decision on when and how a treatment should be instituted, based upon a discussion of risk and possible benefit. The ePOST system does not begin to address this distinction. Lymphadenopathy was the most frequent organ involvement and, along with skin and bone disease, dominates the ePOST score in this study. The final ePOST number amounts to an unsatisfactory amalgam of asymptomatic involvement, morbidity without danger and, in a distinct minority of cases, major and potentially life-threatening organ involvement. In interpreting the observations made by JUDSON *et al.* [1], it matters whether the treatment effect was largely due to improvement in lymphadenopathy and minor organ disease, rather than regression of neurological or cardiac involvement. Unfortunately, the crucial subanalysis, in which major and minor organ disease was evaluated separately, provides no clear answer; trends were significant in neither subgroup. Patients do not present with a nondiscriminatory ePOST score but with a highly individual pattern of organ involvement. The efficacy of many treatment approaches in sarcoidosis depends upon the site and intensity of disease activity. However, in the study by JUDSON *et al.* [1], no statement can be made on this crucial point with regard to infliximab. At best, it can be argued that the similarity of trends between the two organ groupings suggests that the treatment effect may apply across the whole disease range but this conclusion is purely conjectural.

For all its flaws, the study by JUDSON *et al.* [1] has provided useful circumstantial support for physicians who have to do battle with funding bodies to obtain expensive therapies for their patients. This is an increasing concern in clinical practice. There is a paucity of group data with regard to the use of infliximab in sarcoidosis. The quantification of a treatment effect is needed by clinicians but it was, perhaps, unrealistic to imagine that it might emerge in this biased population, given the imperfect tools at the disposal of the group. It is enough to know that a treatment effect exists for extrapulmonary disease because this will encourage empirical exploration of this treatment in aggressive disease, and provides a basis for more definitive studies in the future. However, a routine role for infliximab has not been established by these data. Furthermore, the extrapulmonary Physician Organ Severity Tool system has not been validated in the study by JUDSON *et al.* [1] as a means of quantifying extrapulmonary disease in sarcoidosis. This needs to be understood in order to ensure that the study is not cited in future as a methodological reference.

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