Empiricism in managing Behçet’s syndrome

H. Yazici and G. Hatemi

Although global awareness of Behçet’s syndrome (BS) has appreciably increased, its management still remains largely empirical. We reason that a portion of this empiricism stems from a lack of due attention even among the experts to three important peculiarities of the natural disease course in BS. In a recent exercise to highlight some of the controversies in managing eye disease, 29 ophthalmologists well versed in BS were asked how they would manage a list of paper-patients (1). The undue inattention to age, gender and the duration of disease was most apparent in this exercise in that in none of the 6 case scenarios presented the age nor the sex of the patient was given. Furthermore, precious little information was provided as to at what time during the disease course was therapeutic intervention going to be made. However, we have known for some years now that BS runs a more severe course in the male and in the young and in at least 60% of patients the disease practically goes away after 20 years (2-4). In addition, the most dreaded complication, the eye disease, has its onset mostly within the first year or two (4). Like in almost any biological process there can certainly be exceptions to these generalisations and we surely must be on the alert. However this alertness should not shy us away from considering the more common aspects of the natural disease course in managing BS, as is also true when we attempt to manage any other pathology. The other important component of the prevailing empiricism in managing BS is the simple inadequacy of hard data related to drug treatment, especially related to the management of central nervous system (CNS) involvement and thrombophilia. It is unfortunate that we do not have any controlled data at hand to guide us how to manage, especially the parenchymal type of CNS involvement. Having said that there might be some indication that long-term use of azathioprine has had a beneficial effect on the somewhat better prognosis we have been observing more recently in CNS disease (5).

While there is also a singular lack of controlled studies on how to manage thrombophilia, we perhaps now have more light on how to approach the well recognised problem of the suspected pulmonary emboli in BS. Some long-term students of BS, including our group in Istanbul, have maintained that the frequency of pulmonary emboli were not increased in BS and it was the presence of in situ pulmonary thrombi that were the cause of the clinical and imaging findings which were so frequently confused with genuine emboli. Thus, we did not usually anticoagulate our patients with such a presentation. There obviously has already been some evidence to justify our approach, including the outcomes of 1 retrospective survey (6), one very recent one (7) and a literature review indicating more benefit from immunosuppressives rather than anticoagulation in such patients (8). In addition there was no mention of cases of pulmonary emboli in the largest autopsy series (n=127) of some years ago (9). Finally, it is well recognised that the peripheral venous thrombosis of BS is most commonly in the form of relatively long segments of thrombi adherent to an inflamed vessel wall in contrast to an anchoring head and a free floating tail of the common or garden variety venous thrombosis, a structure intuitively more prone to causing emboli (10).

There has been a further and what we consider an important bit of evidence to back up our contention that the lung thrombi in BS are usually locally formed. In our recent survey of pulmonary vascular disease we had the chance to observe the outcome of some...
EDITORIAL

Empiricism in managing Behçet’s syndrome / H. Yazıcı & G. Hatemi

parenchymal lesions which were initially diagnosed as pulmonary emboli in ventilation/perfusion scans. When the scans were repeated 2 to 6 years later in 6 patients (4 of whom also had peripheral vein thrombosis) the scans continued to show the same abnormalities as in the initial scans (11). In true pulmonary emboli, these lesions would surely have been resolved. It must be underlined however that all this evidence against anticoagulation in BS surely does not replace a true to form controlled study.

We will now turn to discuss the quality, or its lack, of evidence about some of the drugs about which there is more than empirical evidence as to their use in BS.

Colchicine is probably the most frequently and widely used drug in the management of BS. In two randomised controlled trials it was shown to be effective for nodular lesions and joint involvement (12, 13). In the second trial it was also shown to be beneficial in genital ulcers but only among women. Notably it had no effect on oral ulcers in either trial. It is to be noted that no firm conclusions could be drawn from these trials on any possible effect of colchicine on eye disease or the other organ manifestations since they were not part of the target patient groups. In contrast, a double-blind and crossover RCT from Iran reported a significant improvement in oral ulcers, genital ulcers and papulopustular lesions with colchicine, without any gender difference (14). It is quite difficult to critically assess this manuscript in that one cannot follow the number of patients in the placebo and colchicine arms in an orderly manner in the way the data are presented. Nevertheless, in clinical practice one can come across patients reporting that their oral ulcers increased after they stopped colchicine. While it is possible that this represents a placebo effect, it is clear that what is needed is a placebo controlled withdrawal study among those patients who report a beneficial effect. This is particularly important in the light of the fact that the two double-blind studies we had conducted were not powerful enough to exclude a type II error in reporting a beneficial effect in a subset of patients.

It is widely accepted that interferon-alpha is effective in managing eye disease in BS (15). On the other hand, this is mainly based on retrospective data (16). The manuscript reporting on the only controlled experience with interferon-alpha in eye disease of BS has been withdrawn. There are still discussions and repercussions (17). However, what is not widely appreciated is that the design of that study was such that interferon-alpha (along with benzathine penicillin) or placebo was administered to a group of patients with BS and no eye disease for 6 months. There was no difference in either arm with respect to the emergence of eye disease. However, it was after at least 6 months after the interferon-alpha was stopped that patients in the drug arm began to develop significantly less eye disease. This rather interesting and indeed curious state of affairs – especially if we remind ourselves that eye disease in BS usually develops rather shortly after the onset of full syndrome – is most often omitted in discussions about the said manuscript.

There are still important issues that need to be addressed which would make the interferon-alpha use less empiric in BS (16). The best dose, the frequency, the time of onset of action and whether concomitant use of glucocorticoids are desired still wait for more evidence.

Treatment of eye involvement in BS usually starts with azathioprine together with systemic and local steroids during attacks (15). If uveitis attacks continue to recur and/or the visual acuity continues to drop despite this regimen, or adverse events are experienced with these drugs, other treatment modalities are required. There is no consensus on whether cyclosporine-A, interferon-alpha or tumour necrosis factor-alpha (TNF-α) antagonists should be the drug of choice in such patients. Case series and case reports with infliximab in BS patients with uveitis showed that and infliximab acted rapidly, improved visual acuity, improved retinal vasculitis, retinitis and cystoid macular oedema, decreased the frequency of attacks and provided sustained remission as long as it was continued. However, relapses were common after its discontinuation. Open studies and case series with interferon-alpha have also shown beneficial results with high remission rates, reperfusion of occluded retinal vessels, regression of retinal neovascularisation and improvement in the long-term visual prognosis. Moreover, in contrast to infliximab, interferon was shown to maintain long-lasting remissions even after its discontinuation (18). A head-to-head comparison of interferon-alpha and TNF-α antagonists is required to assess which agent should be the drug of choice in such patients. The rapid action of infliximab in BS uveitis, which is reported as early as within 24 hours, is one of its most emphasised advantages (19). However, another agent, cyclosporine-A also improves ocular findings rapidly. There is only one study comparing these two drugs in BS, and it is a retrospective chart review. It was observed that the number of uveitis attacks was significantly lower during infliximab use, but the improvement in visual acuity was similar with both drugs (20). A head-to-head trial with cyclosporine-A and infliximab is also needed to determine whether there is a difference regarding how rapid these drugs act and to compare their efficacy.

Another question regarding the use of TNF-α antagonists is whether the concomitant use of immunosuppressives increases the benefit obtained from these agents. Studies in rheumatoid arthritis patients have shown that concomitant use of methotrexate improves the results, perhaps partly through the inhibition of antibody development against TNF-α antagonists. On the other hand, concomitant disease-modifying agents are usually not prescribed in ankylosing spondylitis patients. A review of the use of TNF-α antagonists in BS suggests that combination of infliximab with azathioprine and/or cyclosporine-A may be better than infliximab monotherapy for obtaining sustained ocular remission (21). However, a randomised prospective trial is also needed to address this issue.

Finally, one cannot help not to rationalise that the paucity and the inadequacy of RCTs in BS might be related to the
Empiricism in managing Behçet’s syndrome / H. Yazici & G. Hatemi

medical practice, research priorities and customs in general of the geographies where BS is also most frequent. In this regard it is sobering also to note that the first RCT with colchicine in BS was, to the best of our knowledge, also the first investigator initiated RCT of any agent in any disease in Turkey. Add to this the recent trend to mistreat the RCT even in very geographies where the RCT was born and flourished we perhaps can better appreciate the dynamics of the prevailing empiricism in managing BS (22).

References