Consensus statement on the future of mannan-binding lectin (MBL)-replacement therapy

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Abstract
Prepared by David C. Kilpatrick on behalf of the speakers and delegates. There follows a consensus statement on the future of mannan-binding lectin replacement therapy to ‘wrap up’ this series of articles.

The future of mannan-binding lectin (MBL) therapy depends on proof of efficacy established by controlled clinical trials. Clinicians are unlikely to request MBL unless it is available as a licensed pharmaceutical product with clear-cut indications that have been established by randomized clinical trials of adequate power. However, plasma fractionaters are reluctant to invest resources in the development of a new product unless there is an obvious, self-evident use for it and a demand for it by clinicians. At present, it seems most likely that future application of MBL therapy may be restricted to a few, carefully selected patients.

MBL insufficiency has been associated with many diseases, sometimes in relation to susceptibility, sometimes as a prognostic factor. For some conditions, the data are inadequate; for others, conflicting data have been reported. In selecting target disorders for MBL therapy it is essential that confirmation of any relationship has been obtained from at least two independent studies; where several investigations have been carried out in the same clinical context without unanimity, a large majority conclusion might be acceptable. Ideally, prospective studies are required to obtain an accurate assessment of predictive value. It is also important to standardize MBL measurements to ensure that different groups are estimating approximately the same amounts and distributions of oligomers.

A second criterion for any clinical trial should be that a clear and objective end-point(s) must be reachable within a relatively short time, preferably within a year.

Thirdly, it would be necessary to recruit sufficient patients in a manageable manner, which in practice might mean within a limited geographical area. It is likely that at least 20 patients would be required for a phase II trial and 100–200 patients for a phase III trial. The exact numbers would obviously depend on the target group and the power calculations based on the strength of association with each target group.

It is very difficult to reach universal agreement about target disorders. It was considered that the above criteria could possibly be met for specified infections in patients with co-existing immunodeficiency secondary to chemotherapy or HIV disease, and also for rheumatoid arthritis patients since radiographic evidence of bony erosions or well-established clinical criteria and chemical markers of inflammatory activity could be assessed. Trials to determine improved lung function in cystic fibrosis patients, or improved live birth rate in women with recurrent miscarriage, might also be feasible.

One potential target group that does not fully match the agreed criteria should be sympathetically considered. Young children who select themselves by presenting on a regular basis with debilitating infections could be entered into a blind, randomized trial to establish if short-term treatment with MBL can break what appears to be a vicious cycle of recurrent infections in which the current infection predisposes to a subsequent infection. Again, an agreed objective end-point would be critical, such as a disease-free period post-treatment (perhaps a year) during which medical attention is not required.

It was generally agreed that proof of principle for any indication should first be established using natural, plasma-derived formulations, and only afterwards should corresponding trials of recombinant MBL be initiated. However, there is no absolute requirement for trials with plasma-derived MBL before trials with recombinant MBL can be initiated.

The implementation of controlled clinical trials is the only way that the physiological significance of MBL will be determined unequivocally. It is not necessary to understand the detailed mechanisms of action of MBL first, and it is recognized that presently unforeseen applications may arise when such trials get under way.

Key words: collectin, innate immunity, mannan-binding lectin (MBL), MBL therapy.
Abbreviation used: MBL, mannan-binding lectin.
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