Clinical potential of mannose-binding lectin-replacement therapy

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Abstract
Mannose-binding lectin (MBL; also known as mannan-binding lectin) is an important component of innate immunity. MBL levels are mainly genetically determined. Low serum MBL levels and their cognate haplotypes have been associated with a wide range of infections. However, most subjects with MBL deficiency remain healthy. MBL deficiency is also associated with non-infectious diseases including systemic lupus erythematosus, rheumatoid arthritis, cystic fibrosis and common variable immunodeficiency. MBL deficiency may affect susceptibility to (e.g. meningococcal disease), or alter the natural history of (e.g. rheumatoid arthritis, cystic fibrosis), a disease. MBL (plasma-derived or recombinant) therapy has yet to be shown to be safe and effective. Potentially it may be useful in MBL-deficient patients to reduce susceptibility to, or enhance recovery from, bacterial infection or to alter the natural history of a disease (disease-modifying drug). In practice the place of MBL therapy may be as a disease-modifying drug to reduce the severity of rheumatoid arthritis and to preserve lung and liver function in cystic fibrosis. MBL therapy may also ameliorate various immunodeficiency syndromes. A potential hazard of MBL therapy is enhanced complement-mediated host damage. The place of MBL therapy will await results of randomized controlled clinical trials.

MBL and innate immunity
The first description of what turned out to be mannose-binding lectin (MBL; also known as mannan-binding lectin) deficiency was a report in 1968 of a young atopic girl with recurrent bacterial infection [1]. This child lacked an inherited plasma factor (opsonin) that was necessary for in vitro phagocytosis of yeast by phagocytes. Furthermore her recurrent infections were ameliorated by infusions of fresh frozen plasma. This was the first indication of the potential value of MBL replacement. Later work showed that the opsonic defect in this child was fairly common in the population and was due to MBL deficiency. MBL is a C-type plasma lectin that is synthesized by the liver and is a component of the innate immune system (for review see [2]). MBL binds to sugars on microbial surfaces and activates two MBL-associated serine proteases to cause complement activation [3]. This is the third complement activation pathway. Human plasma levels of MBL are largely genetically determined. Three different variant alleles coding for structurally abnormal proteins have been identified in codons 52, 54 and 57 of exon 1 of the MBL gene located on chromosome 10q11.2–q21. These structural variants are common in most populations, with combined gene frequencies in Caucasians of approx. 0.21 [4–6]. Individuals who are homozygous or compound heterozygous for variant alleles have plasma concentrations of about 10% of the wild-type levels. Variants in the 5′ flanking sequences of the MBL gene have also been identified. Some promoter haplotypes appear to influence plasma MBL concentrations although this may reflect linkage between promoter polymorphisms and structural variants in exon 1 [7,8].

Consequences of MBL deficiency
Most subjects who are MBL-deficient appear to remain healthy. However, low serum MBL levels and their cognate haplotypes have been associated with a range of bacterial infections in both children [4,9–12] and adults [13]. The wide variety of pathogens involved in these infections is typical of an immunodeficiency. However, the fact that most MBL-deficient people do not get infections had led to speculation that a second immune defect needs to be present for susceptibility to infection. Support for this view comes from observations in several primary and secondary immunodeficiency syndromes. In syndromes as diverse as common variable immunodeficiency (CVID) [14], HIV/AIDS [15] and chemotherapy-induced neutropenia [16,17], the presence of variant MBL alleles is associated with earlier, more frequent and more severe infections. The data from bone marrow transplantation are conflicting [18,19]. An analogous situation is found in cystic fibrosis where the presence of variant MBL alleles is associated with poorer lung function [20,21] and more advanced liver disease [22]. The mucus plugs in the airways and bile ducts that characterize cystic fibrosis are the proximate cause of tissue damage and recurrent infection. Presumably the co-existence of MBL...
Therapeutic Applications of Mannan-Binding Lectin

Table 1 | Possible roles of MBL deficiency

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<thead>
<tr>
<th>Disease</th>
<th>Increases susceptibility</th>
<th>Modifies natural history (effects)</th>
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<tbody>
<tr>
<td>Bacterial infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children [4,9,10,12]</td>
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<td></td>
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<tr>
<td>Adults [13]</td>
<td></td>
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<tr>
<td>Meningococcal disease [11,29]</td>
<td>➤</td>
<td>➤ (milder)</td>
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<td>Pneumococcal pneumonia [30,31]</td>
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<tr>
<td>Parasitic infection</td>
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<tr>
<td>Malaria [32,33]</td>
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<tr>
<td>Viral infections</td>
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<td></td>
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<tr>
<td>Hepatitis B [23]</td>
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</tr>
<tr>
<td>Hepatitis C [34]</td>
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<tr>
<td>Immunodeficiency</td>
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<tr>
<td>CVID [14]</td>
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<tr>
<td>HIV/AIDS [15]</td>
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<tr>
<td>Neutropenic (chemotherapy) [16,17]</td>
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<tr>
<td>Bone-marrow transplantation [18,19]</td>
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<td>Chronic granulomatous disease [24]</td>
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<tr>
<td>Other diseases</td>
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<tr>
<td>Cystic fibrosis [20-22]</td>
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<tr>
<td>Ischaemic heart disease [2]</td>
<td>➤</td>
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<tr>
<td>SLE [2]</td>
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<td>Rheumatoid arthritis [2]</td>
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<td>Recurrent miscarriage [2]</td>
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<tr>
<td>Ischaemia-reperfusion injury (rat) [2]</td>
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Table 1 lists current disease associations with MBL deficiency and includes some further examples where the association is uncertain, due to either paucity of data or conflicting reports.

**Experience of MBL therapy**

The first attempts at MBL replacement used fresh frozen plasma [1,25]. These transfusions corrected the in vitro opsonic defect and seemed to reduce the frequency of infection. Next, two MBL-deficient patients were treated with an MBL preparation affinity-purified from plasma (Cohn fraction III) [26]. This normalized serum MBL levels and complement-mediated opsonization with a half-life of about 6 days. One child had six MBL infusions over a fortnight with no unwanted effects or anti-MBL antibody response. The frequency of infections in this child was dramatically reduced and puzzlingly the improvement was sustained for more than 3 years. Finally, a young MBL-deficient adult with cystic fibrosis and deteriorating lung function received MBL infusions over 3 months [27]. Although her lung function did not improve it appeared to stabilize and deteriorated again when MBL infusions ceased. While these reports of MBL therapy are anecdotal they do give some cause for optimism. It is hoped that a recombinant MBL preparation will soon be available for clinical trials [28]. Recombinant MBL will be
free of concerns over viral contamination and production capacity. However, some questions remain about the efficacy of recombinant MBL. Will recombinant MBL be superior to MBL isolated from plasma or even Cohn fraction III? Both these plasma-derived products contain other immune factors apart from MBL. As discussed above, it is possible that MBL alone is not sufficient to reverse the immune deficiency. Furthermore, MBL exists as a homopolymer of up to 18 polypeptide chains with a distribution of oligomers in the blood. While all oligomers can bind to carbohydrate ligands, only the higher oligomers activate complement. It is presumed that only higher-order oligomers will be of therapeutic value but it is possible that the smaller oligomers may also have a role.

Potential clinical applications of MBL therapy
Here are reviewed the diseases where MBL therapy may be useful. This section is of necessity speculative due to paucity of data. In some diseases it is not yet certain whether MBL even has any role. It is further presumed that the clinical trials will use recombinant MBL whose formulation contains therapeutically appropriate oligomers or mixture of oligomers. This is a deliberately vague definition of the formulation of recombinant MBL because it is not known which size oligomers are needed (complement-activating or non-complement-activating opsonins or both). In general terms, MBL therapy could be used in three clinical scenarios. Firstly, where MBL deficiency leads to increased susceptibility to disease, MBL replacement could theoretically be used to increase resistance to that disease. Secondly, in an acute infection MBL therapy might, by enhancing the immune response, speed the resolution of disease in MBL-deficient patients. However, by analogy with complement deficiencies, MBL replacement in infection might actually do more harm than good by increasing complement-mediated host damage. Thirdly, MBL therapy could be used to alter the natural history of chronic diseases. Such ‘disease-modifying drugs’ are already widely used. A recent example is the use of tumour necrosis factor inhibitors (infliximab, etanercept) to reduce activity and slow progression of rheumatoid arthritis.

Bacterial infections
MBL deficiency appears to cause increased susceptibility to bacterial infections including severe diseases such as meningococcal disease. It is doubtful that MBL therapy will be used in most deficient patients to prevent bacterial infections. Most of these patients will be children and the drug will need to be given by injection over a period of time. A few patients with very high infection frequencies will no doubt be candidates for MBL therapy but in most cases prophylactic antibiotics will probably be sufficient. A note of caution here is that meningococcal disease seemed to be milder in MBL-deficient patients [11]. Therefore MBL therapy could aggravate the course of infection by increasing complement-mediated host damage.

Viral hepatitis/cirrhosis
Immune responses are reduced in cirrhosis for a number of reasons including impaired reticuloendothelial function and blood shunting. SBP is a severe infection that develops in end-stage cirrhosis. An interesting report indicates that SBP is commoner (with an odds ratio of 5) in MBL-deficient cirrhotics [23]. The cause of cirrhosis in these patients was hepatitis B but that is probably irrelevant. Currently antibiotics provide prophylaxis against SBP. SBP is a serious disease and if MBL therapy could prevent it in MBL-deficient cirrhotics this would be a valuable advance. This disease seems a good candidate for a clinical trial of MBL therapy.

Immunodeficiency syndromes
MBL deficiency appears to be associated with an adverse course in both primary and secondary immunodeficiency syndromes. Deficient patients suffer increased frequency of autoimmune disease and earlier, increased frequency of and increased severity of infections. MBL therapy may be useful in these diseases. Although some of these syndromes are rare (e.g. CVID), others are relatively common in hospital practice (e.g. chemotherapy-induced neutropenia). MBL may be useful as a disease-modifying drug in CVID and chronic granulomatous disease, delaying the onset of infections and preventing autoimmune disease. MBL therapy may also be used to increase resistance to infections in deficient patients with chemotherapy-induced neutropenia. Clinical trials would seem to be appropriate in these areas.

Cystic fibrosis
MBL deficiency appears to lead to poorer lung function in cystic fibrosis, presumably due to increased frequency or severity of chest infections. A characteristic liver disease develops in cystic fibrosis that is related to bile duct damage and may progress to cirrhosis. MBL deficiency is associated with cirrhosis in cystic fibrosis patients, implying that it causes more aggressive disease. MBL is now regarded as a disease-modifying gene in cystic fibrosis that contributes to the variegated phenotype of this disease. A clinical trial of MBL therapy in MBL-deficient patients with this chronic disease seems to be clearly indicated. The feasibility of such a trial is another matter. To detect significant differences in survival or rate of development of cirrhosis caused by MBL replacement will require large numbers of MBL-deficient patients followed over many years.
Rheumatoid arthritis

As discussed above, current evidence indicates that MBL deficiency does not contribute to susceptibility to rheumatoid arthritis but may be associated with more severe disease, particularly erosive arthritis. Thus MBL therapy may have a role as a disease-modifying drug and controlled trials would seem to be warranted. However, as discussed above for cystic fibrosis, clinical trials in this chronic disease will probably have to be large scale and extend over years to have the power to detect significant differences.

Recurrent miscarriage

There are reports that MBL deficiency in women is associated with recurrent miscarriage. The association is not strong and some studies have failed to find it (for review see [2]). The role of MBL therapy in recurrent miscarriage seems rather limited for two main reasons. Firstly, the association with MBL therapy is not strong and secondly there is a reluctance to administer any drug, particularly biological agents, to pregnant women. The regulatory issues surrounding another biological treatment for recurrent miscarriage, lymphocyte immune therapy, are instructive (http://www.fda.gov/cber/ltr/lit013002.htm).

Conclusions

The prospect of recombinant MBL becoming available for clinical trials is exciting. MBL in serum is a complex mixture of oligomers. It is not clear how closely recombinant MBL needs to replicate this pattern. It is envisaged that MBL therapy may be used in MBL-deficient patients to either reduce susceptibility to, or enhance recovery from, bacterial infection. MBL may also prove to be a disease-modifying drug in some non-infectious diseases. However, therapy will be restricted to the subset of patients who are MBL-deficient. MBL therapy may reduce susceptibility to SBP in end-stage cirrhosis. MBL may also prove to be a disease-modifying drug in diverse diseases such as immunodeficiency syndromes, cystic fibrosis and rheumatoid arthritis. The logistics of the necessary controlled clinical trials will not be trivial. Large numbers of patients will probably have to be followed for many years to detect significant changes in the natural history of these chronic diseases. Nevertheless the promise seems to be there and the prize is great.

References


Received 20 February 2003