 REVIEW ARTICLE


Disease associations of mannose-binding lectin & potential of replacement therapy

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Mannose-binding lectin (MBL) is an important component of the immune defence able to bind to repeating mannose based structural patterns typical of microbial surface (bacteria, viruses, fungi, parasites) leading to opsonization and phagocytosis, and activation of the complement pathway resulting in lysis of the pathogen. MBL thus plays a very important role in the first line of host immune response. MBL deficiency has been implicated in susceptibility and modulating the severity in viral, bacterial, fungal, and protozoan infections. High MBL levels, on the contrary might be helpful to intracellular organisms, which take the advantage of C3 opsonization and C3 receptor on monocytes/macrophages to enter their host. MBL replacement therapy to help patients with MBL deficiency has undergone phase I clinical trials. Phase II and III trials and production of recombinant MBL for replacement therapy are currently underway.

Key words Innate immunity - mannose-binding lectin - recombinant MBL - recombinant therapy

Introduction

The human collectin, mannose-binding lectin (MBL) is one of the important components of innate immunity1,2. It provides first line of defense by its ability to bind sugar residues on the bacterial surface through its carbohydrate recognition domain and activates the complement pathway leading to lysis of bacteria independent of antibody3. Three point mutations in exon 1 of the MBL gene impair the expression of functional protein leading to a MBL deficient state, which leads to recurrent infections4-7. Once identified, this state could be treated by MBL replacement therapy. MBL isolated from pooled human plasma has been used in phase I clinical trials for replacement therapy. Production of recombinant MBL is under way. This review prouder are over new of the developments in the field.

MBL structure, function, and genetics

MBL, a member of a family of Ca$^{2+}$ dependent collagenous protein8, recognizes a broad range of molecular patterns (e.g. mannose, N-acetylg glucosamine, and fucose residue, etc.)9 typical of microbial surfaces (bacteria, viruses, fungi, parasites) and leads to opsonization and phagocytosis by polymorphonuclear (PMN) cells. This binding also results in activation of the complement system in an antibody in C1q independent manner and requires MBL associated serine proteases MASP-1, MASP-2, MASP-310. Bound MBL associated with MASP-2 was able to promote C4 deposition in a
concentration dependent manner and was able to form C3 convertase that led to formation of membrane attack complex (MAC) and lysis of bacteria. While, MASP-1 does not directly activate the complement system, but recently MASP-1 has been shown to cleave fibrinogen and coagulation factor XIII in vitro, so it may have a role in localized coagulation. No substrate has yet been found for MASP-3.

MBL plays a very important role in the first line of host immune response. The serum MBL level is variable in healthy population. It is known now that the mean serum MBL level in an individual is genetically determined by three single nucleotide substitutions in exon-1 of the human MBL gene located at codons 52, 54 and 57 also referred as D, B, and C mutations whereas the wild type allele is referred as A. These mutations result in amino acid substitution in the collagen-like domain, which results in dominant decreases of functional serum MBL level. In addition, three pairs of allelic dimorphisms can occur in the downstream promoter and the 5′-untranslated region of the mbl-2 gene at positions -550, 221, and +4. The -550 and -221 promoter region polymorphisms form the haplotypes HY, HX, LY, and LX, when inherited in cis with a normal coding region (A). The HYA, LYA, LX haplotypes are associated with high, intermediate, and low serum MBL levels. The combination of structural gene and promoter polymorphisms results in a dramatic variation in MBL concentration in apparently healthy individuals of up to 1000 fold (Caucasian <20-10,000ng/ml). MBL mRNA transcripts are barely detectable in normal liver samples but induction is observed in RNA isolated from human liver that has been exposed to acute stress. The pattern of human MBL synthesis parallels that of two well characterized acute phase reactants C reactive protein (CRP) and serum amyloid A component. This observation supports the inclusion of MBL as an acute phase protein. However, it should be noted that even during an acute phase response, individuals heterozygous or homozygous for MBL mutations appear unable to achieve the protein levels of those possessing a wild type genotype Dean et al. Subsequent studies have shown that MBL levels can increase between 1.5 and three-fold during the acute phase, but this response is variable between individuals of varying genotypes. Approximately one third of Caucasian population possesses genotypes conferring low levels of MBL with approximately 5 per cent having very low levels. Such detailed genotype studies are yet to be done on Indian population. No absolute level of MBL deficiency has been defined. Although a decrease in serum level has been associated with recurrent infection. Serum MBL levels also play a role in modulating the levels of various cytokines in a dose dependent manner.

**MBL deficiency**

MBL deficiency was first recognized in 1968, when a patient with a serum dependent defect in phagocytosis was described. A small girl suffered with severe dermatitis and persistent diarrhoea. Almost no improvement was observed with antibiotic and steroid therapy. Isolated PMN cells from the patient revealed impaired ability to phagocytose heat killed yeast particles from Saccharomyces cerevisiae, rice starch and Staphylococcus aureus in autologous serum, while the same particles were ingested in heterologous serum suggesting a humoral serum dependent defect. Further studies have shown that the particular opsonic defect predisposes to respiratory infection, diarrhoea, atopy and failure to thrive during infancy. The phagocytic defect was linked with lower C3b/iC3b deposition on the surface of yeast incubated in sera of affected individual. Ikeda et al. have shown that MBL could activate complement by the classical pathway. By reconstituting serum defective in opsonization with purified MBL, it was recognized by Super et al. that the C3 dependent opsonic defect is due to lack of MBL. This finding has stimulated many researchers to undertake studies to understand the role of MBL in several diseases.

**MBL binding & bacterial infections**

MBL deficiency has been implicated in susceptibility and course of viral, bacterial, fungal, and protozoan infection (Fig.). MBL binds to a range of clinically relevant pathogens, which were isolated from clinical patients. There is also great variation in the binding of MBL to various organisms; Candida albicans, β-haemolytic group A Streptococci and Staphylococcus aureus bind with high affinity, while Clostridium sp., Pseudomonas aeruginosa, Staphylococcus epidermidis, β-haemolytic streptococci and Streptococcus pneumoniae exhibit low or no binding.

It is also observed that some organisms (e.g. Klebsiella sp. and Escherichia coli) show a variable pattern of binding. Later on it was shown that the absence of sialic acid from the lipo-oligosaccharide (LOS) of Neisseria meningitidis serogroup B, serogroup C and Neisseria gonorrhoeae permits MBL binding and
presence of sialic acid on LOS results in poor or no MBL binding. A similar study was done on Salmonella sp. and it was found that MBL binds to rough chemotype but exhibits low or no binding with smooth chemotype\textsuperscript{37}. Thus, it is clear that lipopolysaccharides (LPS) play a major role in MBL binding to bacterial surfaces. Jack et al\textsuperscript{26} have shown that MBL not only binds to Neisseria meningitidis but also increases phagocytosis mediated by human neutrophils, monocytes, and monocyte derived macrophages, in an \textit{ex vivo} model. Addition of MBL to the blood of MBL deficient donors was found to influence the monocyte derived inflammatory cytokines. The addition of higher concentration of MBL (6 µg/ml) led to a profound decrease in the level of interleukin-6 (IL-6)/IL-1 beta, and tumour necrosis factor (TNF) and vice versa\textsuperscript{26,49}. Recently Bathum et al\textsuperscript{50} described a study conducted in a Danish family with a remarkably high incidence of meningococcal disease in four cases. This study indicates that a combined deficiency of both properdin and MBL increases the risk of infection with \textit{N. meningitidis} and stresses the importance of epistatic genetic interactions in disease susceptibility. These studies clearly show that MBL is not only involved in the complement activation but it is also a potent regulator of inflammatory pathway, and modulates the susceptibility and severity by modulating macrophage interaction with mucosal organisms at the site of initial acquisition\textsuperscript{35}.

**MBL and candida**

Vulvovaginal candidiasis is a yeast infection of the vulva and vagina; millions of women worldwide suffer from vulvovaginal candidiasis\textsuperscript{51,52}. Women with recurrent vulvovaginal candidiasis experience frequent episodes of infection, which result in considerable morbidity and suffering. Several environmental factors have been identified contributing to the recurrent vulvovaginal candidiasis including exogenous hormone, antibiotics, diabetes mellitus, etc\textsuperscript{53}. However, the majority of women with recurrent vulvovaginal candidiasis are not subject to these predisposing factors. It was identified later that women bearing MBL variant allele are at a higher risk for vulvovaginal candidiasis syndrome\textsuperscript{36}. Babula et al\textsuperscript{54} conducted a study on Latvian women with a history of recurrent vulvovaginal candidiasis, and found that these women have significantly lower vaginal MBL levels and an increased occurrence of variant alleles. However, no significant association of susceptibility to chronic disseminated candidiasis in patients suffering from acute leukaemia has been found\textsuperscript{55}. Recently Liu et al\textsuperscript{56} have shown that cervicovaginal lavage (CVL) MBL levels and gene mutation frequency were both higher in women suffering from vulvovaginal candidiasis than in controls. On the other hand, MBL levels were found to be low (0.30ng/ml) in women with recurrent vulvovaginal candidiasis and were associated with a higher gene mutation frequency compare to controls (1.28 ng/ml). MBL binding on the surface of Candida albicans led to agglutination of cells and accelerated complement activation via the lectin pathway, leading to inhibition of growth\textsuperscript{57}. Lillegard et al\textsuperscript{48} have shown that MBL binds to cells which were grown at 37°C but not to cells grown at 23°C. It was also recognized by the same authors that parenteral administration of MBL increased resistance of mice to hematogenously disseminated candidiasis. This finding suggested that MBL plays an important role in innate resistance to candidiasis and MBL therapy may be a means to prevent disseminated candidiasis in high risk patients\textsuperscript{53}, thus suggesting a protective role of lectin complement pathway in female genital tract infection\textsuperscript{59}.

**MBL and HIV**

Many studies have shown that the envelope proteins gp120 and gp 41 of HIV-1 are highly glycosylated consisting of N-linked carbohydrates. The glycosylation provides a formidable barrier for the development of a strong antibody response but at the same time provides a potential site of attack by the innate immune system.
through the MBL. In 1989, Ezekowitz et al had demonstrated the binding of MBL to purified gp120 of HIV. This study reported that MBL purified from the serum is able to bind the infected T cell line H9 but not to uninfected H9 cell lines, while the capacity of MBL to neutralize the virus is less convincing. Recent studies indicate that MBL could opsonize HIV but does not induce neutralization of virus within the physiological concentration range. However, binding and opsonization of HIV may alter virus trafficking and antigen presentation during infection. MBL may also influence the uptake of virus particles by dendritic cells, which express DC-SIGN lectin (dendritic cell-specific intracellular adhesion molecule 3-grabbing non-integrin) over the surface, and has a role in trans-infection of virus to T cells. Pre-incubation of HIV with MBL prevents the trans-infection of HIV of T cells in vitro. The same authors reported that MBL opsonized HIV exhibited a 6-fold higher uptake by monocytes. This observation suggests that MBL could affect the clearance of HIV from blood by binding to virus in vivo and mediating uptake by tissue macrophages that express collagen receptors.

MBL deficiency appears to increase the acquisition of HIV infection by six to eight folds. The mechanism behind this is still unclear. There is evidence of high risk of vertical transmission from infected mother to offspring. In a study done on HIV positive mothers and their children, the frequency of mbl-2 0/0 homozygote was higher in HIV positive mothers than in healthy controls. The mbl-2 0/0 genotype was more frequent in children born from HIV positive mothers than healthy subjects. However, such an association has not been replicated in other populations failing to demonstrate the role of MBL in HIV infection. There is even less clarity in defining the role of MBL in disease progression. Garred et al demonstrated that patients with variant MBL alleles have shorter survival times following the onset of acquired immunodeficiency syndrome than patients with wild type MBL alleles. In another study, Prohaszka et al found that MBL levels were lower in asymptomatic HIV positive individuals compared with HIV negative controls. Patients with high MBL had significantly lower CD4 counts. A possible explanation is that enhanced pro-inflammatory cytokine production in advanced HIV disease may increase the transcription of the mbl-2 gene thereby increasing its level in later stage disease.

In a recent study, it has been shown in vitro that MBL can enhance pro-inflammatory cytokine and viral replication. It was found that the TNF-alpha response significantly increases, when peripheral blood mononuclear cells (PBMCs) of both healthy controls and HIV infected patients were stimulated with MBL and co-stimulated with HIV-1 gp-120. A few studies have assessed the impact of MBL as an antiviral therapeutic molecule. One study has attempted to relate MBL status with HIV infected long-term non-progressors (LTNP). MBL levels consistent with a wild-type genotype were found in six LTNP. Amoroso et al have also shown that children with rapidly progressing disease are more likely to have the variant MBL allele at codon 54 as compared to slow progressors. Vallinoto et al have reported that the presence of variant allele B was associated with higher plasma viral load, suggesting the importance of MBL and its variation in clinical evolution of the HIV-1 infected patients.

Unanswered questions: MBL binds to gp 120 of HIV virus efficiently, but why this binding does not result in neutralization of the virus is not known. It is possible that MBL may help in clearance of HIV virus from circulation but there are no studies showing the rate of clearance of virus by MBL-high and MBL-low individuals. Further, the blocking ability of MBL for the DC-SIGN lectin and the mechanism behind have to be explored. Thus, further studies are needed to understand the mechanism underlying the role of MBL in HIV.

MBL and hepatitis

Hepatitis B virus (HBV) infection is one of the major infectious diseases, with more than 350 million carriers worldwide. It is the most common cause of acute hepatitis and may progress to chronic liver disease including cirrhosis or hepatocellular carcinoma and therefore causes considerable morbidity and mortality worldwide. Progression of chronic hepatitis B and C have been reported to be associated with MBL insufficiency. MBL gene mutation and serum MBL levels were determined in a cohort of Chinese patients who were chronic for hepatitis B or C. Yuen et al found that mutations at codon 54 were more common in patients with symptomatic hepatitis B cirrhosis and in patient with spontaneous bacterial peritonitis (SBP). These findings are helpful in identification of those at risk of developing symptomatic cirrhosis and SBP who may benefit from prophylactic antibiotic treatment. In 2005 Chong et al also reported that MBL genotypes correlating with the low protein levels have a dose-dependent correlation with the occurrence of cirrhosis.
and hepatocellular carcinoma in hepatitis B carriers. It was found that MBL could bind to hepatitis B surface antigen (HBsAg) in a dose- and calcium-dependent, mannan-inhibitable manner in vitro, which clearly shows that binding occurs via the carbohydrate recognition domain. At the same time, Thio et al. showed that MBL genotypes correlating with high serum levels were associated with the recovery from hepatitis B infection, whereas those with lower MBL associated genotypes were associated with the persistence of virus. Similar results were obtained in a study conducted on Vietnamese HBV infected patients with a trend towards higher viral load in those with mutations at codon 5477, which clearly indicates that MBL plays a crucial role in the pathogenesis of hepatitis B. In another investigation, Matsushita et al. studied Japanese patients with chronic hepatitis C responding poorly to interferon therapy. It revealed that patients who were homozygous for the variant allele were less likely to respond to interferon therapy. The same authors also reported that frequencies of LYPB and LXPA, a low promoter haplotype were higher in interferon-resistant patients. Thus, screening of patients with hepatitis B or C will help in identifying those who are at risk of developing cirrhosis and hepatocellular carcinomas44. However, in Chinese hepatitis B and C patients there was no increase in frequency at codon 52, 54, 57 in exon-1 but surprisingly a lower MBL level with respect to controls44. It was concluded that perhaps hepatitis B and C viruses are capable of suppressing MBL production by interfering with the transcription of the mbl-2 gene. Cheong et al. found no correlation of MBL gene polymorphism at codon 54 with either the clearance of hepatitis B virus infection or progression of disease in chronic hepatitis B virus infection. Further work has to be carried out in order to clearly define the role of MBL in hepatitis B and C virus infection.

Non infectious disorders

Mannose-binding lectin gene polymorphism has been associated with a number of autoimmune disorder79. It has been shown that mbl-2 gene variants increased the risk of systemic lupus erythematosus (SLE) in both Chinese and Caucasoid populations80,81. The serum levels of MBL may also influence the risk of several SLE related complications including lupus nephritis82 and arterial thrombosis83. However, one study done by Horiuchi et al. found no association of mbl-2 gene variants with SLE in a Japanese population. Some of the other studies also report the association of MBL deficiency with increased prevalence of rheumatoid arthritis (RA)85. The majority of studies on rheumatoid arthritis show that MBL deficiency is associated with poorer outcome as suggested by clinical, inflammatory, and radiographic studies85,86. MBL has also been shown to be associated with recurrent miscarriage87, preterm birth88, ischaemic heart disease89,90, anti-tumour activity91 against colorectal cell lines. Much detail is still required to understand the role of MBL in non infectious disorders.

MBL paradox

Although MBL deficiency has been studied extensively over the last two decades, the biological role of this lectin in host defence remains to be a matter of debate.

As reviewed above, the absence or low levels of MBL were associated with greater susceptibility to various infectious diseases. However, some of these associations were weak or preliminary casting doubts on clinical significance of MBL deficiency82,93. Contrary to these findings, a population-based longitudinal study showed that MBL deficiency in adults is not associated with a higher risk of morbidity and mortality due to infections94. The clinical manifestation of MBL deficiency seems to be of greater significance either when immune system is still immature as in infancy or when there is an associated immunodeficiency (neutropaenia) due to chemotherapy95.

High levels of MBL have also been considered deleterious to human health because its presence may favour some intracellular organisms, which take the advantage of C3 opsonization and C3 receptor on monocytes/macrophages to enter their host (Fig.). Ambrosio et al. have shown that MBL recognizes the carbohydrate moieties and binds to the surface of Leishmania braziliensis. They provided evidence of antibody-independent activation mechanism of complement pathway. Santos et al. have shown that patients suffering from visceral leishmaniasis had higher levels of MBL than uninfected controls. Another African study suggested that codon 54 mutation afforded protection against both pulmonary and meningal Mycobacterium tuberculosis infection39. A study conducted by Garred et al. on Ethiopian patients with lepromatous/or borderline lepromatous leprosy also found that their MBL levels were significantly higher than those of healthy blood donors. Therefore, any reduction in the complement activating function of the host may reduce the chances of parasitization. An alternative explanation given by Lipscombe et al. was
that the presence of low MBL phenotype may prevent excessive complement activation, which may result in immuno-pathologically mediated host damage. Thus, mutations resulting in decreased levels of MBL will be selected during evolution. These observations have traditionally been interpreted as reflecting a selective advantage of low MBL levels where natural selection has targeted MBL-2 deficiency haplotypes, keeping the frequency of these haplotypes high in population. Seyfarth et al supported the above notion by investigating the molecular mechanism behind the evolutionary loss of MBL expression from lower primates to man, including silencing of the MBL2 gene and the generation of MBL2 variant structural alleles and promoter polymorphism leading to present human MBL2 haplotype. The study clearly defines that MBL2 gene has been repeatedly hit throughout the evolution and silenced eventually by mutation in the glycine residues of the collagen like region, suggesting an evolutionary selection for low expressing MBL genes.

An alternative hypothesis is of evolutionary neutrality. According to this MBL-2 deficiency alleles have no effect on population fitness and can therefore increase in frequency in a random manner. Verdu et al characterized genetic diversity at the MBL-2 genomic region in 1166 chromosome from 24 ethnologically well-defined populations. Their results clearly demonstrated that the pattern of MBL-2 variation was compatible with neutral evolution, as opposed to negative, positive or balanced natural selection, suggesting that high worldwide prevalence of low producing MBL-2 alleles resulted exclusively from the demographic history of human migration and the effect of genetic drift. Boldt et al also found that the diversity seems to have been shaped principally by stochastic evolutionary factors. The evolutionary neutrality of MBL-2 strongly supports the notion that MBL-2 variation does not have strong effect on population fitness, and this lectin is largely redundant in host human defences.

**MBL replacement therapy**

Once MBL deficiency had been identified and MBL became available in therapeutic quantities, reconstitution of patients with opsonic defects and abnormal infections can become feasible. The first MBL product for therapeutic use was isolated from plasma of Danish blood donors by the Statens serum institute (SSI) Copenhagen, Denmark using Cohn fraction III-like starting material based on affinity chromatography on a mannain conjugated matrix. MBL extract was solvent/detergent (S/D) treated by the addition of 1 per cent tween 80 and 0.3 per cent tri - (n-butyl) - phosphate (TNBP) to inactivate viruses. MBL SSI is formulated as a ligand product containing from 250 to 550 µg of MBL/ml depending on batch size and is stabilized by addition of nanofiltered albumin to 5 mg/ml. The final product is available in 3 mg MBL portions. It was shown to have 3 yr stability under cold room storage without change in product characteristics.

The first patient to receive MBL replacement therapy was a two year old girl who had suffered debilitating and recurrent infection from the age of 4 month. She had opsonic defect and very low MBL level. The girl was given daily infusion (2 mg) of MBL for 3 consecutive days and this treatment was repeated after 10 days. The MBL concentration in her blood reached normal values after each infusion and the opsonic activity of her plasma was temporally restored to normal. She remained free from recurrent or abnormal infection during the 8 yr since she received this treatment. The clinical outcome could also be a reflection of the maturation of her immunological memory. It is also a possibility that the MBL infusion may have broken a vicious circle initiated and maintained by a combination of relatively late immunological maturation, MBL deficiency and the recurrent infections since persistent recurrent infection can be considered immunosuppressive.

In another case - control study a 21 yr old, women suffering from cystic fibrosis was referred to Danish CF Center in Copenhagen. She was ΔF508 homozygous. She contracted chronic Pseudomonas aeruginosa infection at the age of 4.5 yr. Her clinical condition was reasonably stable until the age 20, when the dynamic lung function parameters began to decline quite rapidly, with poor and only temporarily benefits from intensified antibiotic treatment and addition of an intermediate dose of systemic glucocorticosteroids (15 mg daily). The patient was found to carry the MBL-insufficient genotype XA/B with undetectable MBL serum levels (<20 µg/ l) and it was decided to try MBL infusion therapy for a tentative period of three-months. (June-September 1988). Over a 3-month period 30 intravenous infusion of purified MBL (Purification was done by Statens Serum Institute) were given, corresponding to a total amount of 172 mg purified MBL. Usually a 6 mg solution of MBL diluted in 100 ml isotonic saline was given twice weakly at an infusion rate of 3 ml per minute, but for a period of 2 wk, alternative doses of 3 and 6 mg were infused. No adverse events were observed at any time. During the first 18 days of treatment, the half-life...
of MBL in circulation was found to be about 2 days. The patient’s lung function did not improve significantly but fluctuated along with the MBL levels during the treatment period. After termination of MBL infusion, the patient experienced a rapid deterioration of her clinical condition, and she died 2 months after cessation of MBL therapy. It appears that MBL may have significant anti-inflammatory effect because of inverse correlation found between serum levels of MBL and the acute phase reactant CRP. This observation was paralleled by an inverse correlation between MBL and proinflammatory cytokine IL-6 level known to induce CRP release. It could be possible that in terminally ill cystic fibrosis patients, MBL substitution therapy achieved serum concentration that correlates with lung function parameters. Thus, MBL therapy may supplement the armory of drugs used to treat cystic fibrosis patients and in other diseases in which MBL deficiency may play a pathophysiological role.

Although no adverse reactions have been observed, support for large scale trials was turned down on the ground that planning for therapeutics based on human plasma was ethically unacceptable. This led to the development of recombinant MBL (rMBL). Jensenius and his group first produced recombinant MBL at the University of Aarhus Denmark. A human endothelial kidney cell line was transiently transfected and cultured in protein-free medium.

Fractionation on mannose derivatized beads allowed purification of oligomers with a distribution compatible with that of plasma MBL. Plasma derived MBL is now being produced by Co-operative Research Centre for Vaccine Technology (CRC-VT) Australia and recombinant MBL by a private industry Natimmune A/S Denmark. In a first ever placebo double blinded study on phase I safety, tolerability and pharmacokinetics, recombinant MBL was administered as both single intravenous (iv) infusion (0.01, 0.05, 0.1, and 0.5 mg/kg body weight) and repeated (iv) infusion (0.1, or 0.3 mg/kg given at 3 days interval). There were no difference in incidence and type of adverse events reported in the study in the subjects receiving recombinant MBL and the placebo group. In addition, there were no clinically significant changes in the laboratory evaluation, ECG or vital sign and no anti-MBL antibodies were detected following recombinant MBL. Administration of recombinant MBL restored the ability to activate MBL pathway of the complement activation. MBL replacement therapy could be used in three different situations. First, where MBL deficiency leads to increased susceptibility of infection, MBL replacement will increase resistance to that infection. Second, in an acute infection MBL replacement may enhance the resolution of the disease by enhancing the immune response in MBL deficient patient. Thirdly, MBL replacement therapy could be used to alter the natural history of chronic disease. Widespread use of MBL replacement therapy will be restricted to a few carefully selected patients until proof of efficacy is established by more controlled clinical trials. It is also possible that some of these predictions may turn out to be wrong and new unexpected uses of MBL may become known.

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