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REVIEW

Cytokine Storm Syndrome

Looking Toward the Precision Medicine Era

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Introduction

"Cytokine storm syndrome" is a diverse set of conditions unified by a clinical phenotype of systemic inflammation, multi-organ failure, hyperferritinemia, and, if untreated, often death. This clinical constellation is caused by the elaboration of extreme amounts of inflammatory mediators resulting from unchecked feedforward immune activation and amplification. The initiating factors leading to the end state of cytokine storm are heterogeneous and derive from rheumatologic, oncologic, and infectious origins.

The first member of the cytokine storm family to be recognized by physicians was sepsis. The appreciation that the consequences of sepsis are a result not of the pathogen, but rather the immune response to the pathogen, dates back to observations made by William Osler in 1904 in his book, *The Evolution of Modern Medicine*. Accordingly, the idea that sepsis might be most effectively treated by immunomodulation is not new. With the identification of tumor necrosis factor (TNF) and interleukin-1β (IL-1β) as major inflammatory cytokines in models of sepsis in the last part of the twentieth century, trials were undertaken to block these cytokines to treat septic cytokine storm. The failure of blockade of these molecules to improve outcomes in sepsis (1–3) dampened enthusiasm for this approach for many years. In addition to the timing of therapeutic intervention (i.e., patients were typically not enrolled in the clinical trials at an early enough time point for immunomodulation therapy to potentially be successful), these trials likely failed because the situation is more complicated than Osler first recognized, with complex host–pathogen interactions playing a role beyond the simple notion that sepsis is due solely to an excessive immune response.

Further complicating matters, cytokine storm cannot be considered a disease itself, but rather the common end point of different initial insults: infectious, autoimmune/inflammatory, and iatrogenic. Even within those broad categories significant differences exist, making the landscape unlikely to be amenable to a "one-size-fits-all" therapy. Quite the opposite, we are approaching the beginning of a new era of precision medicine for cytokine storm, in which understanding of the immunologic derangement of each individual trigger, and perhaps in each individual patient, will inform the choice of intervention.

Success in personalization of therapy will require the practitioner to consider the similarities and differences in a wide array of conditions under the moniker of "cytokine storm." Common to the cytokine storm syndrome, and exemplified by all of the diseases discussed here, is a loss of negative feedback on the immune system, resulting in the overproduction of inflammatory cytokines. In turn, these inflammatory cytokines drive a positive feedback on their own production, begetting the common syndrome of exponentially growing inflammation and multi-organ failure. Commonly, but not exclusively, the main effector cytokine in these syndromes is interferon-γ (IFNγ). In contrast, distinguishing these diverse syndromes are the initial triggers that set off this chain of events, as well as the individual cytokines responsible for the loss of negative feedback and gain of positive feedback

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leading to the amplified response. In this review, we will outline the advances made in basic investigation into pathogenesis of cytokine storm syndromes of genetic, autoimmune/inflammatory, and iatrogenic causes and then discuss how such advances have informed therapy, moving from empiricism to the more finely tuned "precision" approaches.

Pathogenesis of cytokine storm syndromes

Monogenic cytokine storm syndrome. The most progress in understanding of cytokine storm has been made in familial hemophagocytic lymphohistiocytosis (FHLH), a genetic syndrome caused by deficiency in cytotoxic cell function. Deficiency in perforin or in molecules essential for perforin vesicular transport and release results in infection-triggered cytokine release and the resultant multi-organ inflammation and other pathology characteristic of cytokine storm. The monogenic nature of FHLH makes it amenable for study in animal models using targeted mice with deletions in genes discovered in humans. This work has identified IFNγ as a causative cytokine in generating the multi-organ pathology leading to mortality in this disorder (4,5). In FHLH, IFNγ is produced in excessive amounts by cytotoxic CD8+ T cells that are unable to kill infected target cells due to the absence of perforin activity or delayed cytolytic granule depolarization (6). This in turn results in prolonged contact with target cells (7) and subsequent inability to eliminate them (ultimately preventing the signal for producing IFNγ from being terminated), and release of excessive amounts of cytokine. This IFNγ release is not due to the inability to clear the pathogen itself, but rather is the result of altered antigen presentation due to the inability of cytotoxic cells to prune the antigen-presenting cell populations correctly (8). Both neutralization of IFNγ and depletion of CD8+ T cells have been shown to ameliorate disease in murine models (4,5).

Given the strong evidence of a central role of IFNγ in FHLH, it has been tempting to speculate that this cytokine has a role in all cytokine storm syndromes. Both in patients and in animal models of disease, however, multiple scenarios have been observed in which features of cytokine storm syndrome develop in the absence of IFNγ or its receptor (9–11), indicating that the causes are more complex that just this single cytokine. It has also been argued that similar mechanisms of ineffective cytotoxic cell killing are responsible for cytokine storm in non-FHLH settings (12–14). However, the diverse array of rheumatologic conditions that can lead to cytokine storm, not necessarily associated with defects in perforin function, make such a simple model unlikely.

Autoimmune/inflammatory cytokine storm syndrome. Among rheumatic diseases, systemic juvenile idiopathic arthritis (JIA) and its adult analog, adult-onset Still's disease (AOSD), have the highest association with cytokine storm. In this context, cytokine storm is often called macrophage activation syndrome (MAS), a reference to activated macrophages often seen on tissue biopsy, despite lack of evidence that these cells cause the syndrome (although they do, at least under some circumstances, produce inflammatory cytokines) (15). The cause of MAS in systemic JIA and AOSD remains unclear. Some work suggests that, at least in a subset of patients, there are defects in perforin function, although not of the same magnitude as seen in FHLH (14,16). These data are confounded by inflammatory activity (17) and treatment effect, both of which alter cytotoxic cell killing, particularly when measured with standard natural killer cell cytotoxicity assays. Whole exome analysis has suggested that patients with systemic JIA, and in particular those who have had an MAS episode, are more likely to have a variant in FHLH-associated genes (12). Nonetheless, such findings represent only ~35% of patients with systemic JIA–MAS, indicating that the majority do not have alterations in genes known to be associated with FHLH. Although this percentage may in fact be shown to be higher as additional genes are identified and noncoding mutations are accounted for, recent data call into question whether there is any defect at all in natural killer cell cytotoxic function in systemic JIA (18).

While the pathogenesis of systemic JIA and associated MAS has not been elucidated, a role of cytokines in at least some patients has been established. In a report published in 2005, IL-1β was identified as being dysregulated in systemic JIA, leading to the successful use of anakinra, an IL-1 receptor antagonist, as therapy (19). Subsequent randomized controlled clinical trials have shown efficacy of IL-1 blockade in large populations of patients with systemic JIA (20). IL-6 was additionally recognized as a potential target, with large trials showing efficacy of blockade of its receptor (21). However, neither IL-1β nor IL-6 has been directly linked to the development of MAS. Rather, elevated IL-18 levels have been associated with the predisposition to MAS development in patients with systemic JIA (22,23), as well as with MAS from various secondary causes (24). IL-18 blockade improved some parameters of organ dysfunction in an FHLH mouse model, though ultimately not reducing mortality (25). Intriguingly, IL-18 receptor signaling has been shown to be defective in systemic JIA (26), although this phenomenon has not been studied in great detail in patients who have had MAS. It is therefore difficult to resolve precisely how IL-18 might contribute to MAS associated with systemic JIA, given this apparent conflict between elevated IL-18

levels in MAS and defective IL-18 receptor signaling. One possibility is that suppressed IL-18 receptor signaling in systemic JIA is a compensatory mechanism that prevents progression to MAS; when this mechanism fails, and there is a large amount of IL-18 present, MAS ensues.

Additional evidence supporting the notion that IL-18 has a role in autoinflammatory MAS comes from the recently described NLRC4-MAS syndrome (27,28). NLRC4-MAS is caused by an activating mutation in the NLRC4 inflammasome. Unlike patients with inflammasomopathies not associated with MAS, such as activating NLRP3 mutations, patients with NLRC4-MAS develop high levels of serum IL-18, suggesting a potential causal link. NLRC4-MAS is anticipated to be an excellent genetic model to provide additional insights into possible etiologies of cytokine storm, as studies of patients with this genetic defect exhibit no concomitant abnormalities in perforin function or cytotoxicity. Placing IL-18 into the pathogenic model of systemic JIA–MAS remains consistent with the established pathogenic role of IFNγ in cytokine storm, given that IL-18 is well known to result in IFNγ production by many cells. Thus, pathogenic IFNγ may arise either from a more proximal defect in perforin cytotoxicity as in the case of FHLH, from overproduction of IL-18 in autoinflammatory conditions, or from yet-to-be-defined defects in immune regulation in other settings. Recent evidence of elevated levels of IFNγ and IFNγ-responsive genes in systemic JIA with MAS is consistent with the notion of the importance of IFNγ, even in systemic JIA–MAS (29).

MAS has been associated with other rheumatic diseases, including systemic lupus erythematosus (SLE) (30), Kawasaki disease (31), spondyloarthritis (32), and juvenile dermatomyositis (DM) (33). As these are rarer disorders than systemic JIA–associated MAS, reports are scarce and systematic studies are limited. There are presumably multiple different underlying mechanisms across this diverse range of diseases, although systemic inflammation remains a common link. The development of lupus pancreatitis appears to be associated with risk of MAS (34), although a causal link has not been established. In the case of SLE-associated MAS, serum TNF levels have been reported to be elevated with normal serum levels of IL-18, suggesting a qualitatively distinct cytokine pattern from that in systemic JIA–MAS and therefore, a distinct pathogenic mechanism. On the other hand, the same activating polymorphism of IFN regulatory factor 5 that has been associated with risk of SLE conferred a 4-fold increased risk of MAS development in patients with systemic JIA (35), suggesting common pathogenic links. In the case of juvenile DM–associated MAS, serum IL-6 and IL-18 concentrations were reported to be elevated, declining as disease improved, also suggesting some common features with systemic JIA–MAS (36). To comprehensively compare and contrast these MAS phenotypes in different rheumatic diseases, prospective multicenter efforts with collection and study of larger numbers of specimens will be necessary.

Iatrogenic cytokine storm syndrome. Iatrogenic causes of cytokine storm can also be informative as these cases are, in a sense, controlled experiments from which mechanistic insights can be gained. The entire list of iatrogenic causes of cytokine storm is too extensive to enumerate, but they range from pharmacologic, as in the case of rituximab therapy (37), to procedural, such as cardiac bypass (38). The recent use of chimeric antigen receptor (CAR) T cells for the treatment of CD19+ B cell malignancy is a striking example in which patients develop a cytokine storm referred to as cytokine release syndrome (CRS) (39). A detailed dissection of the mechanisms by which CAR T cells induce CRS is beyond the scope of this review. Studies suggest a few key points related to the mechanism of CRS following immunotherapy (39–42): 1) lysis of sufficient targets is required, whether they be tumor or normal endogenous B cells; 2) diverse targets may be sufficient for CRS, as 2 distinct antigenic CAR T cell–directed therapies have been shown to cause CRS; and 3) both macrophages and IL-6 appear related to the development of CRS. The extent to which the mechanisms of CRS may relate to FHLH or MAS is unknown, and further work to test these mechanisms should be undertaken.

Treatment of cytokine storm syndromes

Put in simplest terms, treatment of cytokine storm syndromes consists of immunosuppression accompanied by attempts to control the underlying trigger or disease. In the case of genetically defined syndromes in which replacement of the hematopoietic system with genetically normal bone marrow would be "curative," allogeneic bone marrow transplant also plays an important role. In rheumatic disease–associated cytokine storm, treatment of the underlying disease is essential. Clearly, antimicrobial agents are warranted for any patient with an infectious trigger. With increased understanding of disease mechanisms and the ever-expanding armamentarium of biologic agents and other treatments that inhibit specific pathways, targeted therapy for the various cytokine storm syndromes is becoming a reality.

A discussion of the management of every cytokine storm variant is beyond the scope of this review. Rather, we will review the evidence, from both human studies and animal models, for various classes of immunomodulating therapies, underscoring the value of structured mechanistic investigations to inform a rational treatment approach. We note both the "blunt tools"

Table 1. Cytokine storm syndromes*

Syndrome	Pathologic effectors	Potential precision therapy
FHLH	CD8+ T cells, IFNγ, IL-33	T cell inhibitors, IFNγ neutralization, IL-33 receptor blockade
EBV-HLH	Viremia, IFNγ	B cell–depleting therapy
Systemic JIA–MAS	IL-1β, myeloid cell autoinflammation, IFNγ	IL-1β blockade, IFNγ neutralization
NLRC4-MAS	IL-18, IL-18–induced IFNγ	IL-18 binding protein, IFNγ neutralization
Non–systemic JIA–MAS	Unknown	Unknown
CRS	IL-6, macrophages	IL-6 receptor blockade, IL-6 neutralization
Sepsis	Heterogeneous and multifactorial	More precise geno- and phenotyping required

* FHLH = familial hemophagocytic lymphohistiocytosis; IFNγ = interferon-γ; IL-33 = interleukin-33; EBV-HLH = Epstein-Barr virus–associated HLH; systemic JIA–MAS = systemic juvenile idiopathic arthritis–associated macrophage activation syndrome; CRS = cytokine release syndrome.

originally used empirically for their general ability to suppress the immune system and the "sharper tools" of rationally selected immunomodulators that have begun to herald an era of "precision medicine" for cytokine storm. As this approach continues to advance, it is worth remembering that the terms "MAS" and "cytokine storm" refer to a common end point of multiple different underlying conditions, rather than a single disease. We therefore call attention, where it exists, to evidence for each therapy for use in specific subsets of cytokine storm (Table 1). Investigators conducting future trials should bear in mind this heterogeneity and test therapies in select subsets, rather than in MAS as a whole.

Corticosteroids. As with most inflammatory disease, cytokine storm can be treated effectively with corticosteroids. The specific choice of agent often varies between syndromes and disciplines. Methylprednisolone, used in most rheumatic diseases, has been the most widely reported in treatment of MAS, whether associated with systemic JIA or with SLE. In contrast, dexamethasone is often used in the treatment of FHLH and is the recommended agent in the widely used FHLH treatment protocol (43). It has been argued that dexamethasone has better central nervous system penetration than other corticosteroids and is therefore preferred in FHLH. However, consideration should also be given to effective corticosteroid equivalency of the various regimens, as the reported methylprednisolone-based regimens are often 20-fold more potent than the reported dexamethasone-based regimens. The side effect profile of corticosteroids is well known, and much effort has been—and continues to be—dedicated to finding other agents that can spare the need for extended periods of high-dose steroid treatment.

Cytoablation. The oldest approach to steroid sparing is cytoablative therapy, which is aimed at removing the specific cells that may be driving cytokine storm. In reports of systemic JIA– and SLE-associated MAS, cyclophosphamide was noted to have potential efficacy (30,44). Likewise, in FHLH, etoposide has been a mainstay of therapy for >20 years (43). More recently, studies of animal models of FHLH demonstrated that these drugs work by selectively destroying activated CD8+ T cells (45), consistent with the central role of these T cells as IFN producers in FHLH pathogenesis. No such data exist for other cytokine storm syndromes, and the fact that these drugs are capable of eliminating multiple immune populations likely contributes to their widespread use and efficacy in treating cytokine storm of multiple etiologies and association with a spectrum of underlying diseases.

B cell ablation with rituximab has been observed to have efficacy in Epstein-Barr virus (EBV)–associated HLH (46). The proposed mechanism is reduction in the reservoir of cells for EBV infection and replication, thereby reducing viral load. It should be noted, however, that EBV has tropism for other immune cells, including natural killer cells and T cells, particularly in EBV-HLH and chronic active EBV (47). As a case in point, one of us has had personal experience with an EBV-HLH patient who had an initial reduction in viral load with rituximab therapy, only to have a rebound in viremia shortly thereafter. Flow cytometric sorting of various immune populations revealed that the virus had indeed infected non–B cell populations, thereby escaping the rituximab therapy (Behrens EM, Teachey DT: unpublished observations).

T cell ablation with antithymocyte globulin has been reported both in the treatment phase and in the conditioning for bone marrow transplant phase of FHLH therapy, as well as in MAS (48). In the case of FHLH, depletion of the pathogenic CD8+ T cells presumably contributes to the effectiveness of T cell ablation. A formal trial of antithymocyte globulin in combination with etoposide and dexamethasone (the Hybrid Immunotherapy for

HLH [HIT-HLH]) trial has recently been completed in FHLH, and results are forthcoming.

Alemtuzumab has also been reported to be effective in both FHLH (49) and SLE-associated MAS (50). Alemtuzumab is a monoclonal antibody that depletes cells bearing the CD52 marker, which includes all lymphocytes as well as some myeloid cells, such as monocytes and dendritic cells. It is therefore potentially more potent than more lineage-specific cytoablative antibodies, but at the cost of more potent immunosuppression and infection risk.

T cell–directed immunomodulation. Given the central role of CD8+ T cells in FHLH, nonablative inhibitors of T cell function are also attractive therapeutic choices in this subset of cytokine storm. Cyclosporine and other calcineurin inhibitors work by blocking key signaling pathways downstream of the T cell antigen receptor, thereby preventing the production of IL-2, a cytokine that is essential for T cell survival and proliferation. Thus, cyclosporine blunts the magnitude of T cell responses, making it a rational choice for treatment of T cell–mediated diseases. It has been a part of FHLH therapy for >20 years (43) and has also been used in MAS associated with a number of rheumatic diseases (30,51), although no formal trials have been conducted in this population.

Abatacept, an Fc fusion protein designed to bind and inhibit CD28 signaling of T cells, is another potentially attractive approach. CD28 is critical for providing the "second signal" for robust T cell activation. A small case series of 4 patients with systemic JIA, including 2 with "mild MAS" with disease refractory to standard intervention (including IL-1β blockade), demonstrated responsiveness to the addition of abatacept to the treatment regimen (52). This finding suggests that abatacept therapy may be efficacious, perhaps in combination with IL-1β blockade; however, more formal study is needed to validate its use in this condition. Enthusiasm may be tempered by the report of a rheumatoid arthritis patient in whom EBV-HLH actually developed while the patient was receiving abatacept therapy (53). Notably, virtually every medication used to treat MAS has also been reported to cause MAS. In these MAS cases, it is difficult to determine precisely whether the drug or the underlying rheumatic disease was the true trigger; thus, caution must be applied when interpreting such reports.

IFNγ blockade. Targeted cytokine therapy has resulted in a dramatic change in the landscape of treatment of immune disorders. With the identification of IFNγ as a necessary cytokine for the development of FHLH in murine models (4,5), there has been much excitement about the use of agents to block this cytokine for the treatment of human disease. Further enthusiasm has been generated by a recent report of elevated IFNγ signals in patients with systemic JIA–MAS (29). At the time of preparation of this manuscript, a trial is underway to test IFNγ-neutralizing therapy in FHLH. Results are not currently available, but individual patient outcomes reported in abstracts suggest promise for this approach (54). Safety concerns are always important and may be informed, in part, by reports of naturally occurring IFNγ-neutralizing autoantibodies in some patients (55). Serious mycobacterial infections occur in such patients, suggesting that long-term treatment with IFNγ-neutralizing antibodies may be limited by such complications. Pending the results of the ongoing trials, IFNγ blockade may indeed become a rational therapeutic modality.

Blockade of IL-1 family member cytokines. The IL-1 family cytokines are composed of related proteins, including IL-1β, IL-18, and IL-33, all of which are of interest in cytokine storm syndromes. IL-1β has received the most attention, as approved drugs have been available to block this cytokine. There have been numerous published case reports and case series supporting the use of IL-1β blockade in MAS associated with various rheumatic diseases (56,57). At least in the case of systemic JIA, use of IL-1β blockade in MAS may reflect the principle of treating the underlying disease as a trigger. Consistent with this, multiple authors have suggested an "occult MAS" phenotype in systemic JIA (58,59); that is, patients with systemic JIA may have elements of MAS without the full severe MAS phenotype. If MAS is indeed along the spectrum of severity of systemic JIA disease activity, it should logically follow that therapies known to treat systemic JIA should also treat MAS. Contrary to this notion is the observation that ongoing treatment of systemic JIA with IL-1β blockade does not appear to prevent the onset of MAS, despite the efficacy of IL-1β blockade in reducing disease activity (60). However, because those trials were not powered to detect prevention of MAS and revealed a trend toward protection that did not reach statistical significance, this question remains open.

At a minimum, there are at least some patients in whom IL-1β blockade does not prevent MAS. Ascertaining why this subpopulation is different at the immunologic level could prove enlightening with regard to both pathogenesis and treatment approaches. In some patients, increasing the dosage of anakinra was effective in controlling previously refractory MAS (61,62), suggesting that perhaps in some cases it is actually tachyphylaxis to IL-1β blockade that results in the apparent lack of efficacy. Alternatively, it is possible that the ability of anakinra to block IL-1α is important for its efficacy at higher doses. This would have important implications with regard to the use of canakinumab to treat or prevent MAS, since this drug is selective only for IL-1β. To

date, IL-1 blockade remains untested in FHLH, but given the likely differences in pathogenesis between systemic JIA–MAS and FHLH, there is no specific reason to suspect that IL-1 blockade may have efficacy in this disorder.

As discussed above, IL-18 levels are elevated in patients with systemic JIA who are prone to MAS. IL-18 exists in equilibrium with IL-18 binding protein, in which bound IL-18 is inactive and free IL-18 is active. Measurements of free IL-18 have not been reported in patients with systemic JIA–MAS. However, a pediatric patient with NLRC4-MAS and highly elevated serum levels of free IL-18 was recently reported (63). The child had been treated unsuccessfully with numerous therapies, including IL-1β and TNF blockade. Treatment with compassionate-use recombinant IL-18 binding protein (tadekinig alfa) resulted in complete resolution of symptoms and normalization of laboratory values, even after withdrawal of other medications including steroids. Although this was only a single-patient experience, the dramatic response suggests that cytokine storm syndromes characterized by elevated levels of free IL-18 might benefit from such a therapy, and this warrants further investigation.

Although IL-33 is also an IL-1 family member, it is distinguished by not being a product of the inflammasome, but rather is an alarmin, a molecule that is constitutively expressed but released only upon necrotic cell death. Based on its role in driving "type 2 immune responses" characterized by Th2 CD4+ T cells, eosinophils, and the cytokines IL-4, IL-5, and IL-13, most clinical focus on IL-33 has been on atopic disease, with trials in asthma underway. However, a role of IL-33 in IFNγ production by CD8+ T cells was recently reported (64) and, likely related to this, blockade of IL-33 protects against mortality and morbidity in a murine model of FHLH (65). The safety risks of IL-33 blockade may not be as serious as those of IFNγ blockade, making this an attractive therapeutic strategy for human disease. Just as the murine model has provided preclinical rationale for ongoing trials of IFNγ neutralization in FHLH, IL-33 may also be an important target for FHLH. Furthermore, a report of patients developing FHLH-like syndromes despite having genetic mutations that result in the absence of the IFNγ receptor (11) suggests that it will be important to develop other therapeutic targets beyond IFNγ.

IL-6 blockade. Paralleling the logic behind the use of IL-1β blockade in systemic JIA–MAS, the efficacy of IL-6 blockade with the IL-6 receptor–blocking antibody tocilizumab in systemic JIA might also make this an attractive target for MAS. Unfortunately, as in the case of IL-1β blockade, IL-6 blockade does not seem to prevent the development of MAS in systemic JIA. Other authors have suggested that while IL-6 receptor blockade does not prevent MAS, it may mask its appearance by subduing the laboratory changes that normally occur in MAS (66), creating a greater challenge for the treating physician by confusing the clinical picture. Distinguishing "masked MAS" from "partially treated MAS" is somewhat arbitrary and difficult, though, and an alternate explanation is that IL-6 blockade has an incomplete ability to treat MAS. Further investigation will be needed to clarify this point. However, it is clear that IL-6 is not the central cytokine in systemic JIA–MAS, even if blocking it has a partial effect.

In complete contradistinction to systemic JIA–MAS, the CRS associated with CAR T cell therapy appears to be completely dependent on IL-6. Using tocilizumab to treat patients with CAR T cell therapy–induced CRS results in a dramatic reversal of the syndrome and has become part of the protocol for its management (67). This serves to further highlight that, while clinical end point presentations of cytokine storm syndromes may be similar, the driving forces in their initiation and propagation may differ dramatically.

TNF blockade. TNF initially appeared to be an attractive target for cytokine storm of sepsis, despite its failure in actual clinical trials. Undoubtedly, TNF blockade is an important therapeutic modality for treatment of inflammation associated with a number of rheumatic diseases, and so the possibility remains that, as with IL-6, selection of the correct subpopulation of cytokine storms may be critical. Case reports describing patients in whom TNF blockade successfully treated—as well as reports describing patients in whom it caused—systemic JIA–MAS can be found (68–70). There have been no systematic investigations into the use of TNF blockade in MAS or FHLH, and, given that other targets currently seem more promising, further investigation of TNF blockade in cytokine storm will likely be of lower priority.

JAK inhibition. JAK/STAT signaling is a common mechanism used by many different cytokine receptors, including IFNγ. With the recent clinical availability of inhibitors of JAK signaling for rheumatoid arthritis, consideration of repurposing these drugs for treatment of cytokine storm seems natural. Studies by 2 different groups showed efficacy of JAK inhibition in murine models of FHLH and MAS (71,72), providing important preclinical evidence supporting this approach. Whether the effects of JAK inhibition can be accounted for solely by IFNγ blockade has not been resolved. The attraction of inhibition of JAK signaling is that multiple cytokine–receptor pairs can be targeted simultaneously, obviating the need to know the specific cytokines essential in any particular scenario. Furthermore, the oral bioavailability of these small-molecule drugs makes their use in long-term therapy more tolerable

to patients than injectable medications. However, the obvious tradeoff of the first benefit is the greater possibility for on-target, but deleterious, side effects due to the blockade of multiple pathways at once, as opposed to targeting of a single cytokine or receptor. Indeed, plasmapheresis, another modality that can remove multiple cytokines concurrently, has also been reported as a successful modality in treating cytokine storm (73), providing additional support for this approach.

Conclusions

Much progress has been made in understanding the mechanisms that initiate and propagate cytokine storm. Data from animal models have informed the development and deployment of novel cytokine-blocking strategies in humans and have ushered in the possibility of repurposing existing drugs to treat cytokine storm. Continued focus on fundamental mechanisms, coupled with human observational and interventional studies, will allow us to more precisely define in which populations and in which phase of their disease these therapies will be most effective. Indeed, returning to Osler's original observation about the role of the immune system in sepsis, the results of the original "failed" trial of IL-1β blockade in sepsis were recently reanalyzed to focus only on the subgroup with elevated levels of ferritin, akin to FHLH/MAS (74). In this subgroup, IL-1β blockade had a beneficial effect that had been lost in the analysis of the entire cohort. Undoubtedly, such post hoc analyses are fraught with potential confounders (75); however, the findings in that study emphasize that the time is ripe to reconsider immune-directed therapy for even this "oldest" of cytokine storms. A precision medicine approach, achieved by understanding the immune mechanisms that lead to cytokine storm in subpopulations, and perhaps even individual patients, is likely to yield benefits in other heterogeneous groups of patients with cytokine storm, such as those with systemic JIA or SLE. Continued basic, translational, and clinical investigation will be needed to make such an approach possible. Fortunately, the pace at which new investigations are being conducted and reported suggests that if support for these efforts continues, we can succeed at achieving this.

AUTHOR CONTRIBUTIONS

Drs. Behrens and Koretzky drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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