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Anti-TNF Therapies in Rheumatoid Arthritis, Crohn's Disease, Sepsis, and Myelodysplastic Syndromes

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ABSTRACT An attempt has been made in this article to summarize the state-of-the-art clinical experience with the use of anti-TNF therapies in four diseased states with special emphasis on myelodysplastic syndromes. Given the central role of TNF-α in initiating and perpetuating the chronic damage produced in the diseased organs by controlling a cascade of pro-inflammatory cytokines, as well as its acute role in sepsis, theoretically speaking, neutralization of this peptide was a natural therapeutic choice. Results of the initial clinical trials appear encouraging and sometimes dramatic in their efficacy. The mechanism of response however, is interesting in that even when TNF-α is directly targeted by a monoclonal antibody, the resulting benefits can frequently not be attributed to TNF suppression alone. Rather, it appears that a more general effect on the T-lymphocytes is also contributing to the responses being seen. This raises the new possibility of combining anti-cytokine and anti-T-cell strategies to treat at least the more chronic diseases such as Crohn's disease and myelodysplastic syndromes. Continued clinical trials testing these strategies are clearly warranted. *Microsc. Res. Tech. 50:229–235, 2000.*

INTRODUCTION

Parsimony in nature is graphically manifested in the frequent employment of a single pathway for multiple, often opposing functions. One prime example of this cross-functionality is provided by the ubiquitous, multi-purpose cytokine, tumor necrosis factor alpha (TNF-α).While diseases may not share a common etiology, a plethora of signs and symptoms experienced in states as disparate from each other as rheumatoid arthritis (RA), multiple sclerosis (MS), acquired immune deficiency syndrome (AIDS), cancer, septic shock, congestive heart failure (CHF), and hematopoietic disorders such as aplastic anemia (AA) and myelodysplastic syndrome (MDS) have been directly attributed to the excess production of a single cytokine, TNF-α (Cannella and Raine, 1991; Cannon et al., 1990; Dezube et al., 1995; Feldmann et al., 1996; Hober et al., 1989; Koike et al., 1995; Perrault and Menasche, 1999; Raza et al., 1996a–c; Selmaj et al, 1991; Shetty et al., 1996). The fact that one protein is capable of mediating the danger signs of so many maladies depending upon the cytokine cascade it initiates, the organ involved, the cells in question, the etiologic agent that is operational, and whether the irritation is acute or chronic has only recently been appreciated in some totality, and clearly represents the tip of the iceberg. Overproduction of TNF-α may be acute and intense, or chronic and low-grade, each carrying its own set of unique manifestations. The grave consequences of extremely high TNF-α levels such as those seen acutely in septic shock are related to two major effects of this pro-inflammatory cytokine. Along with Interleukin-1 (IL-1), it serves as a "proximal" master initiator of the cytokine cascade, which helps perpetuate septic shock, and, secondly, the more "distal" end-organ damage that so often proves to be irreversible and fatal (Porter, 1997). However, the more subtle consequences of chronic, low-level elevations are far more obscure and difficult to decipher, regularly defying scrutiny and only recently becoming the subject of systematic study. These include the role of TNF-α in causing the signs and symptoms of chronic diseases such as RA, AIDS, MS, AA, and MDS. Attempts to suppress both the acute and chronic elevation of TNF-α are, therefore, only as old as the recognition that this peptide is the principle mediator of the disease manifestations related to a variety of pathologic states. In other words, the field is in its infancy. The success of anti-TNF or anti-cytokine approaches in vitro and in animals have more recently been translated into human trials with some equivocal and occasional dramatic outcomes. Until the precise mechanisms of response are understood, both the successes and the failures must be taken with a grain of salt and extreme caution must be exercised in ascertaining that the baby is not thrown out with the bathwater. The purpose of this article is to briefly review anti-TNF therapies in general, with special reference to the preleukemic disorders grouped under the heading of myelodysplastic syndromes or MDS.

ANTI-TNF THERAPIES AVAILABLE

There are basically three approaches to suppress the activity of TNF-α that have been utilized in clinical trials so far. The first is to use antibodies to TNF and these include the chimeric monoclonal antibody cA2 or Infliximab/ Remicade (Centocor) and the humanized antibody of the IgG4 isotype CDP571 (Celltech/ Bayer).

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TABLE 1. Anti-TNF therapeutic agents

Drug	Company	Status
1. Etanercept	Immunex	FDA approved
2. Lenercept	Hoffman-LaRoche	Developmental
3. Infliximab	Centacor	FDA approved
4. CDP571 humanized moab against TNF	Celltech	Developmental
5. Thalidomide	Celgene	FDA approved
6. Pentoxifylline	Hoescht-Roussel	FDA approved
7. IL-10	Schering	Developmental
8. Amiodorone	Wyeth-Ayerst	FDA approved

An extension of this approach is to block the transcription factor NFkB believed to function upstream of TNF-α, critically controlling the onset and perpetuation of the inflammatory process. A second approach to neutralize the activity of TNF-α is based upon providing the soluble TNF-α receptors in vivo. Enbrel or p75 TNF-R:Fc (Immunex) and lenercept, p55 TNF-R:Fc (Roche) are examples of this therapy. Finally, agents known to interfere with the signaling pathways of a variety of cytokines simultaneously though less specifically, can nonetheless be quite useful, especially in combinations. These include drugs such as pentoxifylline, thalidomide, and dexamethasone. See Table 1 for details. The following review will concentrate upon the in vivo use of these agents in a variety of human diseases.

RHEUMATOID ARTHRITIS

It has been appreciated for at least two decades that cytokines lie at the heart of chronic inflammatory and autoimmune diseases. In the case of RA, all cytokines were found to be expressed in the joints, suggesting that a key aspect of chronic diseases may be the continuous production of cytokines, as opposed to the transient one seen in response to antigen presentation. It was rapidly learnt that most of the destruction in the joints of RA patients was mediated via IL-1. Since TNF-α regulates IL-1 activity, it was no surprise to discover that both TNF and TNF receptors were upregulated in the joints of patients with RA (Buchan et al., 1988; Chu et al., 1991; Di Giovine et al., 1988). This led to attempts to neutralize TNF-α and thereby ameliorate the ongoing IL-1 mediated joint destruction. At least in vitro it was found that a successful suppression of TNF-α was simultaneously accompanied by an inhibition of IL-1, granulocyte macrophage colony stimulating factor (GM-CSF), IL-6 and IL-8, suggesting that the proinflammatory cytokines are not independently regulated, but controlled as a module or coordinate (Brennan et al., 1989; Haworth et al., 1991). Once again, it was no surprise that the critical coordinator of this cytokine cascade was none other than TNF-α, and IL-1 to a lesser extent (Butler et al., 1995). Prior to the discovery that TNF-α often provided the password that sets the cytokine cascade into motion, these inflammatory mediators were considered poor therapeutic targets because of their redundant and overlapping roles. The modular functionality of the cascade capable of being switched on and off by a master peptide changed all that. Following the in vitro work on cultured RA cells, animal studies were undertaken centered on the concept of downregulating the inflammatory cytokine module by neutralizing TNF-α activity in an animal model of RA, collagen-induced arthritis. Both joint inflammation and joint destruction were found to be reduced, even if administered after the onset of disease (Piguet et al., 1992; Thorbecke et al., 1992; Williams et al., 1996) human trials soon followed. A chimeric anti-TNF-α antibody called Infliximab (Centocor) produced encouraging results (Elliott et al., 1993) and led to many confirmatory studies with other antibodies. These include CDP571 (Celltech/Bayer), enbrel, p75 TNF-R Fc (Immunex/AHP), lenercept, p55 TNF-R Fc (Roche), and D2E7 (Knoll/CAT) (Feldmann et al., 1998; Weinblatt et al., 1999). Overall, these therapies were well tolerated in general. Since most trials focused on RA patients with severe disease, doing badly on existing therapies with reduced life expectancies and other morbidity, it is unfair to compare the efficacy of this approach with standard therapies especially when used in patients with less aggressive disease. That said, it is remarkable that the advantages of anti-TNF approach have been so widespread. The benefits are striking and reproducible, representing a decided addition, if not improvement, on currently employed therapies. It is equally important now to see whether these results improve further as the duration of treatment is prolonged over the 6-month trials initially employed and if this approach serves patients with less severe disease better than standard options. Trials with other agents such as pentoxifylline have not produced as encouraging results as the antibodies or the use of soluble receptors (Dubost et al., 1997). A new approach being proposed now is to try blocking signals upstream of TNF-α such as the transcription factor NFkB that may be driving the inflammatory process (Bondeson et al., 1999; Wang et al., 1996) and this is being attempted via delivery of signals through vectors such as adenoviruses. In other words, with the development of the concept, and then the successful demonstration of cytokine manipulation to control the signs and symptoms of a chronic disease like RA, we have officially entered the truly exciting, modern era of genetic engineering.

CROHN'S DISEASE

Although the incidence of this idiopathic chronic inflammatory bowel disease is increasing in Western Europe and the United Stateas, the cause remains unknown. Intestinal (bacteria) antigens, T-lymphocytes, and cytokines play the key roles in the pathogenesis of these disabling, life-long disorders (Fiocchi, 1997; Powrie, 1995). Increased TNF-α levels lie at the center of the cytokine abnormalities (Breese and McDonald, 1995), making the TNF neutralizing strategy particularly attractive. Infliximab or the cA2 monoclonal antibody was the first in this series of agents to produce encouraging and often dramatic results (Hanauer, 1999; Prescent, 1999; Rutgeerts and Paert, 1999; Targan et al., 1997; Van Dullermen et al., 1995). Following its approval for use in Crohn's disease by the FDA in 1998, it has now also received positive advice for the Europeans Evaluation Agency in 1999. Infliximab acts rapidly, clinical improvements becoming apparent within 5 days of starting the treatment, and lasting for 10–12 weeks in most patients. Further investigation into the mechanism of Infliximab action yielded new insights into the pathogenesis of Crohn's disease. It had been demonstrated that mucosal T-lymphocytes in

Crohn's disease are apoptosis-resistant (Biorivant et al., 1999). Infliximab was shown to increase the ratio of Bax (pro-apoptotic) and Bcl-2 (anti-apoptotic), resulting in an increased rate of programmed cell death in previously activated Jurkat T-lymphocytes in vitro (Ina et al., 1999). These data suggest that in addition to its direct anti-TNF activity, Infliximab may also have important anti-inflammatory effects by targeting activated T-lymphocytes. This is not the first time an agent has produced the desired effect in an unpredictable manner. A precise understanding of the mechanism of action of anti-TNF agents will doubtless lead to the development of more effective therapies. The positive clinical experience with Infliximab has opened the door for trials with other anti-TNF agents in Crohn's disease. The humanized CDP571 antibody has shown efficacy in this disease and other TNF-neutralizing strategies are being tested in clinical trials now (Stack et al., 1997; Van Deventer, 1997).

SEPSIS

Endotoxins in septic states lead to an outpouring of TNF-α from monocytes and macrophages resulting in the clinical manifestations of septic shock (Beutler et al., 1986). Suppression of TNF-α in this setting should theoretically lead to a dual benefit (Hinshaw et al., 1990). On the one hand, it should interrupt the cytokine cascade being proximally initiated by its activity, and, on the other hand, prevent the end-organ damage being mediated distally (Hinshaw et al., 1990). In animal studies, blocking TNF-α effects after experimentally producing septic shock has been highly effective in reducing both morbidity and mortality (Tracey and Cerami, 1993). It must be remembered however, that in animals, septic shock is produced acutely in otherwise healthy animals with TNF-α, while actual septic shock in humans usually is the end-stage manifestation of an enormously immunocompromised and, usually, chronically ill patient with previous multi-organ disease already present (Blackwell and Christman, 1996). To begin with, therefore, a comparison of anti-TNF therapies in these two situations is plagued by widely different starting points. It is no surprise then that at least two clinical trials using anti-TNF monoclonal antibodies have failed to show a significant benefit in 28-day all-cause mortality in patients with sepsis (Abraham, 1998; Abraham and Wunderink, 1995; Cohen and Carlet, 1996; Porter, 1997). A trend in improved survival was observed in the subgroup of patients with severe sepsis, including those with dysfunction of two or more organ systems or with septic shock associated with the dysfunction of at least one organ system (Abraham, 1998), and, therefore, the final word on the efficacy of suppressing TNF activity in septic shock must await the results of larger multi-center trials presently underway. Other approaches such as IL-1 receptor antagonist administration to septic patients is also being tested (Fisher et al., 1994).

MYELODYSPLASTIC SYNDROMES or MDS

A particularly interesting paradox has been described in the baffling; heterogeneous hematopoietic disorders grouped under the umbrella of MDS (Heaney and Golde, 1999). Besides the dysplastic morphology, the hallmark of this stem cell disease, which generally affects the elderly, is a variable peripheral cytopenia in the face of cellular bone marrows (BM). Given the monoclonal nature of the disease (Janssen et al., 1989), it is clear that the initial abnormality strikes a pluripotential stem cell, an event that confers a proliferative advantage on the transformed cell leading to an unchecked clonal expansion (Raza et al., 1996a–c). The robustness of this clone is such that eventually a monoclonal hematopoiesis is established with all blood cells including the B-lymphocytes and monocytes sharing a single parent ancestral cell (Prehal et al., 1978). The unexpected finding in view of the obvious intramedullary fitness of the rapidly dividing clone is the inability of the maturing daughter cells to survive and make it to the periphery. A series of studies designed to investigate the cellular dynamics of the bone marrows in MDS patients have been conducted in the last decade and have led to some rather interesting insights into the pathogenesis of this disease. Briefly, using sophisticated in vivo labeling of S-phase cells by the thymidine analogs iododeoxyuridine and/or bromodeoxyuridine (IudR and BrdU, respectively), we were able to show that there is increased proliferative activity in the marrows of MDS patients with large numbers of cells actively synthesizing DNA (Raza et al., 1997). Peripheral cytopenia in the face of this actively proliferating BM was shown to be the result of excessive cytokine-mediated intramedullary apoptotic death of maturing hematopoietic cells (Raza et al., 1995). The two major pro-apoptotic cytokines were subsequently identified as being IL-1b (Mundle et al., 1996) and TNF-α (Shetty et al., 1996). In other words, the very cytokines driving the rapid proliferation of the expanding clone were also responsible for causing the innocent bystander death in their daughters. A new paradigm for MDS was proposed thereafter, which can be summarized as follows (Raza et al., 1996). An as yet poorly understood event or series of events transforms an early hematopoietic progenitor, leading to clonal expansion and eventual monoclonal hematopoiesis. In this setting, pro-inflammatory cytokines such as TNF-α serve the dual function of stimulating the proliferation of the dividing cells and inducing apoptosis in their maturing progeny. We further proposed that if this model is correct, then suppression of the responsible cytokine would also lead to a dual benefit, on the one hand an improvement in the cytopenias should be apparent as the maturing cells stop apoptosing, and, on the other hand, removal of the cytokine providing the stimulus for the proliferation of the MDS clone should lead to its regression with eventual restoration of polyclonal hematopoiesis. Rarely have insights into the biology of a disease become translated into improved therapies for the patients with such alacrity as was accomplished in the case of translational research conducted in MDS. In just the last 4 years, a series of clinical trials have been completed to test the efficacy of anti-cytokine therapies in improving the cytopenias experienced by MDS patients. These will be summarized briefly here.

Pentoxifylline (PTX), Ciprofloxacin (Cipro), and Dexamethasone or PCD Therapy With or Without Amifostine

Initial attempts to suppress TNF-α were undertaken using the rather non-specific drug PTX, which is known to interfere with the second messenger pathways of a

variety of cytokines including TNF-α, IL-1β, and transforming growth factor beta (TGF-β) as well as its activity in downregulating the mRNA for TNF-α. Cipro was simultaneously used to block the hepatic degradation of PTX by interfering with the P450 reductase system and dexamethasone was added with the intent of potentiating TNF-α suppression since it is known to inhibit the translation of mRNAs into proteins. The first clinical trial yielded a response rate of approximately 40%, however no complete responses were observed (Raza et al., 1998). The patients with partial responses generally showed improvements in the cytopenias that have been reported in detail elsewhere. An unexpected finding was the observation of occasional disappearance of karyotypically abnormal cells. Since cytogenetically marked clones could only be eliminated with cytotoxic therapies thus far, their disappearance in response to anti-cytokine therapy made this approach even more attractive. Furthermore, regression of these clones in response to anti-cytokine therapy also provided direct and incontrovertible proof that these clones were dependent for their proliferative advantage on the cytokines being suppressed in vivo by therapy. Occasionally these abnormal metaphases disappear despite continued presence of MDS, suggesting that within the marrow of an individual MDS patient, there is continuous evolution of competing clones, some of which are more fit to survive than others. These evolving clones are obviously driven by the cytokine whose suppression led to their disappearance, whereas the parent clone may be dependent for its proliferation on cytokines other than those being neutralized or being cytokine independent completely and autonomously driven. Thus, this first study confirmed many of the hypotheses proposed to explain the complex, paradoxical pathology of MDS in a direct, in vivo setting. In the next study, PCD was combined with the cytoprotective agent amifostine to attempt further improvement in the clinical outcome of patients (List et al., 1997). This combination resulted in a response rate of approximately 60%, which was better than that seen with either therapy alone (Raza et al., 1999a,b). Unfortunately, in both clinical trials, it was impossible to precisely define the mechanism of improvement in the hematopoietic indices since multiple agents were employed in each study and none of the drugs were specifically targeting any particular cytokine. Despite this limitation, we were able to show that the mechanism of action is cytokine related since responders showed the most sustained reductions in TNF-α levels (Reza et al., 1998). Obviously, the real test of the efficacy of anti-TNF therapy in ameliorating the cytopenias of MDS patients can only come when this cytokine is directly suppressed by using antibodies or soluble receptors described for RA and Crohn's disease earlier. These studies are described below. Nonetheless, the early, albeit modest, success of these clinical trials established the feasibility of this approach and paved the way for the development of an entire new area of therapeutic research based upon the principle of cytokine modulation to improve the cytopenias in MDS.

Enbrel

In an attempt to directly test the proposition that the pathognomonic cytopenias in MDS patients are cytokine, and more specifically TNF-α mediated and that neutralizing TNF-α levels in these patients will result in improvements in the blood counts, TNF-α receptor Enbrel was administered in vivo to these individuals (Raza et al., 1999). A dimer of two monomers of the extracellular p75 TNF receptor fused to the Fc portion of a type I human immunoglobulin (TNFR:Fc) has been marketed by Immunex under the brand name, Enbrel. We administered Enbrel at a dose of 25 mg/dose twice weekly to 20 MDS patients for a period of 12 weeks. Of the 20 MDS patients, 9 were in the refractory anemia (RA) category, 5 had RA with ringed sideroblasts (RARS), and 6 had RA with excess blasts (RAEB) according to the French-American-British (FAB) classification. The median age was 67 years, there were 9 females and 11 males, and all patients had primary de novo MDS without a prior history of toxic or chemical exposure. Enbrel was remarkably well tolerated in this group of patients with no serious adverse events. Two patients experienced a rash at the injection site. A total of 18 patients were able to complete the twelve weeks of therapy prescribed and were available for response evaluation. There were no complete responders, which is defined as the return of all peripheral blood indices to normal as well as normalization of the blast count in the BM. Partial responses (PR) were defined as one of the following: (1) Reduction in red cell transfusions by at least 50% or an increase in hemoglobin by at least 2 Gm/dL; (2) Increase in absolute neutrophil count (ANC) by 500/μl over the baseline; and (3) Increase in platelet count by 30,000/μL over the baseline. Amongst the 18 evaluable patients, 10/18 showed a partial response. Two patients had a trilineage response while the rest either had a bilineage response or responded in a single lineage. Of the 10 responders, 2 showed a >50% reduction in transfusions, 8 had a greater than 30,000/μL increase in the platelets, while 6 had a >500/μL increase in ANC. The increase in ANC was statistically significant when responders were compared to non-responders ($P = 0.051$). Patients who had a higher pre-therapy biopsy cellularity tended to respond better than those who had a hypocellular BM (median cellularity 80% vs. 40%, respectively, $P = 0.033$). Thirteen patients presented with abnormal cytogenetics while 7 had a normal karyotype prior to starting therapy. The most frequent cytogenetic abnormality was that affecting chromosomes 5 and/or 7 (5 patients), while one had trisomy 8, three had deletions of 20q, and four had other non-specific karyotypes. It was interesting to note that 5/7 patients with normal cytogenetics showed a PR whereas 7 of the non-responders had an abnormal karyotype. Responding patients belonged to all different FAB categories. In summary, therefore, it appears that suppression of TNF-α using the soluble receptor can indeed have profound biological effects in MDS patients and that some of these effects can clearly be translated into clinical responses as well. The patients most likely to respond are those having normal cytogenetics and a hypercellular BM, indicating that the pathogenesis in MDS patients with abnormal karyotypes and/or hypocellular marrows may be more complicated, with the cytokine-driven component playing a less critical role in these patients than in the case of MDS with normal cytogenetics and a hypercellular marrow. Another possibility is that the predominant abnormality in the non-responders may reside in the autonomously proliferating

stem cells rather than being the result of a major contribution from any single cytokine. Given the heterogeneous nature of MDS, it is not too far-fetched to assign a variety of etiologies to the variable cytopenias encountered. Finally, the types of responses seen in this pilot study also warrant further comment. Anemia is the hallmark of disease in MDS and gross morphological abnormalities of the erythroid series in the bone marrow are the rule. Yet, the majority of patients who responded to Enbrel, albeit partially, showed an improvement in platelets (8/10) or in ANC (6/10), while only 2/10 responders had a reduction in transfusion requirements but without any substantial increase in their hemoglobin levels. The precise reason for this is unclear at the moment, but it is very possible that this only indicates an inadequate duration of therapy, with partial improvement in the less serious cytopenias becoming apparent earlier than the more profound ones.

Thalidomide

In addition to a cytokine-mediated excessive intramedullary apoptosis of hematopoietic cells, the bone marrows of MDS patients have also been found to show increased angiogenesis, and higher than normal levels of vascular endothelial growth factor (VEGF) (Pruneri et al., 1999). Thalidomide would be a natural choice for MDS patients since this drug both suppresses TNF-α and inhibits neo-angiogenesis (Klausner et al., 1996). A pilot study has been conducted in MDS patients using thalidomide as a single agent at a starting dose of 100 mg po hs and increasing as tolerated to 400 mg po hs (Raza et al., 1999). Therapy was continued for at least 12 weeks and further in responding patients or continued at the discretion of the investigator. Thirty-three patients were accrued on the study at the time of writing and 20 patients are evaluable for a response. Ten patients have demonstrated a partial response according to the criteria described above, while no patient had a complete response. The median age for this group was 69 years. As per FAB classification, 20 patients had RA+RARS, 12 had RAEB, and 2 had chronic myelomonocytic leukemia (CMMoL). Of the 10 responding patients, 8 demonstrated an erythroid response, 4/10 showed a platelet response, and one had improved ANC. The therapy was quite well tolerated. The most important thing about the responders was the fact that three long-term transfusion dependent individuals (1, 3, and 3 years) all of whom had refractory anemia became transfusion-independent and their hemoglobin levels showed an increase as well. Companion biologic studies conducted to examine the mechanism of response have failed to identify either a definitive suppression of TNF-α levels or a decrease in angiogenesis as being consistently associated with a response. In other words, although there is a general tendency for both the TNF-α levels as well as micovessel density to decrease in the post-therapy marrows of the majority of treated patients, these biological effects do not necessarily translate into a clinical response. It must be noted that the protocol is still accruing patients and that these conclusions are by no means final. A curious observation, however, is the matter of occasional "delayed" responses being seen with this approach, which suggest that thalidomide may be exerting some of its actions via immune modulation. In one case, hemoglobin continued to improve 100 days after therapy began, and in another, following little improvement during a 12-week course of thalidomide and 10 weeks after termination of therapy during which the patient only received supportive care, a trilineage response gradually set in. These effects are reminiscent of anti-thymocyt globulin (ATG) induced responses in aplastic anemia where it can take as long as 6 months after the administration of ATG for a response to become apparent (Teramura and Mizoguchi, 1996). In fact, ATG has now shown activity in MDS as well (Molldrem et al., 1997) and it is very likely that at least in some patients, thalidomide and MDS are producing a response via the same mechanism of T-cell suppression. In summary, therefore, thalidomide appears to be an exciting new addition in the therapeutic armament of anti-TNF therapies, and specifically brings some long-awaited good news to the MDS cases for most of which supportive care has remained the "standard" treatment of choice to date.

SUMMARY OF THE RATIONALE AND RESULTS OF ANTI-TNF THERAPY IN MDS

Myelodysplastic syndromes are baffling hematopoietic disorders whose precise etiology continues to evade researchers. The disease is more common in the elderly and in those exposed to chemicals (such as benzene), and toxic agents such as chemotherapies for a prior malignancy. While abnormalities of chromosomes 5 and/or 7 are common, especially in those with secondary MDS, yet there is no proof to date that these abnormalities are etiologically related. Rather, they appear to represent derivative populations and evolving clones since they usually constitute a sub-population of cells in an otherwise monoclonal BM. There is increasing suspicion that these states may represent a chronic inflammatory response rather than a true malignant disease (Raza, 1998a,b). An infectious etiology has also been proposed with some intriguing initial observations implicating the herpesviruses as possible culprits in at least some of the MDS patients. However, disease association awaits further proof and research (Mundle et al., 1999). In this context, a cytokine-based repertoire of signs and symptoms assumes yet another significant dimension. As noted in the section on rheumatoid arthritis, TNF-α can play the role of the master switch that turns a cascade of cytokines on and off, causing much chronic pathology and end-organ damage. A similar scenario in MDS can be visualized where a perpetual ongoing inflammatory process in the bone marrow could result in the selection of a clone capable of cytokine-driven rapid proliferation, whose eventual expansion would lead to monoclonal hematopoiesis, while cytokine-induced innocent bystander death of maturing hematopoietic cells would result in a variable cytopenia. Beautiful hypotheses have a nasty habit of being unraveled by ugly facts. In this case, however, the very first pilot study using rather non-specific drugs (PCD) to suppress a variety of pro-inflammatory cytokines produced exciting responses giving credence to the proposed new model of MDS that the major signs and symptoms of the disease were cytokine-mediated. Thus, with the etiology of MDS still shrouded in mystery, it became possible to provide substantial palliation to individual patients with non-cytotoxic therapies aimed at attempting to normalize the cytokine milieu in the bone marrow, thereby restoring the proliferative

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