

The long road to optimal management for chronic granulomatous disease

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Chronic granulomatous disease (CGD) is a prototypic defect of neutrophil function caused by gene mutations affecting the activity of the nicotinamide adenine dinucleotide phosphate (NADPH) complex and resulting in impaired production of microbicidal reactive oxygen species.¹ The most common form of CGD is inherited as an X-linked trait (XL-CGD) and reflects mutations of the *CYBB* gene encoding for the gp91^{phox} subunit of the NADPH oxidase complex. Autosomal recessive (AR) forms (AR-CGD) are due to mutations of the genes that encode for the p22^{phox}, p47^{phox}, p67^{phox}, and p40^{phox} subunits. The disease is characterized by increased susceptibility to recurrent and severe infections of bacterial and fungal origin and a high rate of inflammatory complications, including inflammatory bowel disease; granuloma formation in the liver, lungs, and skin; and inflammation leading to strictures that affect the gastrointestinal and urinary tracts. In the absence of treatment, the disease has a high mortality rate early in life.^{2,3} There is substantial evidence that the severity of clinical manifestations of the disease reflects the degree of residual (if any) NADPH oxidase activity,⁴ which can be readily measured by using the dihydrorhodamine test. The relative distribution of XL-CGD versus AR-CGD varies depending on the geographic context. In the United States approximately 65% of the patients have XL-CGD. Deficiency of p47^{phox} accounts for 20% of all cases, and p67^{phox} and p22^{phox} defects have been identified in 5% of patients each.³ By contrast, AR-CGD has a higher prevalence in areas with a high consanguinity rate.⁵ Previous studies had shown that AR-CGD is often characterized by delayed clinical onset and a higher survival rate than XL-CGD.⁶

The best line of treatment for patients with CGD is still a matter of contention. Medical management based on prompt and aggressive diagnostic work-up and treatment of active infections, rigorous use of antibacterial and antifungal prophylaxis (and possibly of IFN- γ), and judicious use of steroids in patients with

granuloma and other autoimmune manifestations is effective in reducing the risk and rate of severe complications^{1,2} but does not provide a definitive cure, which can be provided by allogeneic hematopoietic cell transplantation (HCT). Initial results of HCT in patients with CGD were often controversial, but improved outcome with robust and stable myeloid chimerism has been reported more recently.⁷ Moreover, use of reduced-intensity conditioning regimens has decreased the risk of transplantation-related complications. However, limited information is available when comparing the long-term outcome of patients treated by medical management versus HCT. Consequently, which patients (and when in the course of disease) would benefit most from HCT is still a matter of debate. Finally, gene therapy would have several theoretic advantages over HCT, including prompt availability of the patient's own hematopoietic stem cells, with no risk of graft-versus-host disease. However, lack of sustained gene marking in the myeloid compartment in early trials resulting in negligible functional correction of the disease and serious adverse events (myelodysplasia and acute myeloid leukemia) caused by insertional mutagenesis have been reported.⁸

Two recent articles published in the *Journal* offer important contributions on controversial aspects of the disease. Koker et al⁵ have reported on the clinical, genetic, and functional characterization of 89 Turkish patients with CGD. In this series XL-CGD accounted for a minority (38.2%) of the patients. Careful genetic and functional characterization of the defect allowed the authors to attempt correlation between the severity of the clinical phenotype on the one hand and the nature of the genetic defect or residual functional activity on the other. All 17 patients with p47^{phox} deficiency included in this study showed residual NADPH oxidase activity; by contrast, all 31 patients with XL-CGD and the vast majority of patients with AR forms other than p47^{phox} deficiency belonged to the oxidase-null group. This difference in residual functional activity had important consequences on the natural history of the disease. In particular, 82.4% of patients with XL-CGD presented with clinical symptoms at less than 1 year, whereas only 50% of the patients with AR-CGD had such an early onset. Mean age at the time of laboratory diagnosis was significantly higher in patients with the p47^{phox} defect (7.32 years) than in patients affected with XL-CGD (2.72 years) or the oxidase-null p22^{phox} (3.8 years) or p67^{phox} (3.3 years) defects. Moreover, severe infections (*Aspergillus* species-induced pneumonia, suppurative lymphadenitis, and deep-seated abscesses), chronic lung disease, and failure to thrive were significantly more common in patients with oxidase-null than in those with oxidase-residual activity. By contrast, no differences were observed in the frequencies of autoimmune/inflammatory complications, anemia, and occurrence of BCG-itis. Severe infections (especially of fungal origin) were the leading cause of death. Eight of the 9 deceased patients included in the study had absent oxidase activity. The probability

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of survival at 20 years was significantly worse (0.38) for patients with oxidase-null than those with oxidase-residual (0.63) activity. Of note, 6 patients in this series received HCT from matched related donors, and all of these were reported to be alive and well.

In another study Cole et al.⁹ took advantage of a nationwide CGD registry in the United Kingdom to compare clinical outcomes between 32 patients who received conservative (ie, medical) management and 30 patients who received curative (ie, HCT) treatment. In this study XL-CGD accounted for 85% of the cases. A significantly higher rate of infection events was recorded in patients treated conservatively (or before transplantation in those who received HCT) than after transplantation. Also, patients undergoing transplantation had improved growth. Forty percent of the patients had colitis, a proportion that is significantly higher than in previous series^{6,10}; of note, no colitis events were reported after transplantation. In spite of these results, which suggest a lower incidence of serious complications after HCT, overall survival was comparable in the 2 groups, and 90% of the patients not undergoing transplantation were reported to be alive at 15 years of age, which was similar to what was reported in a large nation-wide registry study in Italy.¹⁰

Although both studies are important, they also have limitations. The study by Koker et al.⁵ is significant because it confirms and extends recent observations by Kuhns et al.⁴ that clinical outcome in patients with CGD is strictly associated with the degree of impairment of NADPH oxidase activity. Moreover, this article provides information on a relatively large number of patients with AR-CGD and clearly confirms that p47^{phox} deficiency is often characterized by delayed onset and less severe clinical manifestations, which is consistent with residual functional activity. However, methods for retrospective clinical data collection in this study were not detailed. Furthermore, in spite of antimicrobial prophylaxis, survival probability at 15 years was approximately 80%, which is significantly lower than what was reported by Cole et al.⁹ and in other recent studies.¹⁰ Although the reasons for this discrepancy are not clear, it is possible that differences in inclusion criteria (particularly the age of affected subjects) and the availability of diagnostic and therapeutic resources might have played a role. On the other hand, the study by Cole et al.⁹ has the merit to attempt comparison of outcomes between patients treated conservatively versus those who received curative treatment. Superior efficacy was demonstrated for HCT in preventing serious complications and improving growth. Similar results had been observed in a smaller series of patients with CGD in Sweden.¹¹ Moreover, comparison of quality of life in patients undergoing transplantation and those treated conservatively showed better outcome in the former.¹² Although these observations would support the use of HCT, at least in severe cases of CGD, no firm conclusions can be drawn about long-term morbidity and mortality, considering the relatively short duration of follow-up in the study by Cole et al.⁹ Moreover, only a minority of the patients included in this study were genotyped, and data on NADPH oxidase activity were not uniformly available. This made it impossible to match patients in the transplantation and nontransplantation subgroups for oxidase activity, an important predictor of outcome.^{4,5}

Defining the natural history of the disease for patients with CGD born in the last decade (after demonstration in 2003 of

itraconazole efficacy in preventing severe fungal infections)¹³ and comparing outcomes after conservative versus curative treatment in patients with similar levels of oxidase activity is of outmost importance. This will necessarily require a large, collaborative, multicenter study. The Primary Immune Deficiency Treatment Consortium has recently developed a protocol to conduct an observational study that should help address these issues by recruiting a large number of patients with CGD in North America.¹⁴ In consideration of differences in survival observed in the studies by Koker et al.⁵ and Cole et al.,⁹ it would be important to enlarge such natural history studies to include patients living in other areas of the world. In this regard, collaboration among patient advocacy groups and national and international primary immune deficiency societies would be essential.

Finally, measurement of NADPH oxidase activity has emerged as a key biomarker that might help predict outcomes in patients with CGD, yet there is uncertainty whether patients with absent functional activity should be referred to HCT early in life or only after the first significant manifestations of disease. This decision might also be influenced by progress in transplantation and, hopefully in the near future, gene therapy.⁸

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