Genetic Factors in Clozapine-Induced Agranulocytosis

Ilya Reznik MD and Roberto Mester MD

Ness-Ziona Mental Health Center, Ness-Ziona and Sackler Faculty of Medicine, Tel Aviv University, Israel

Key words: clozapine-induced agranulocytosis, major histocompatibility haplotypes, mortality risk

IMAJ 2000;2:857–858

For more than a decade scientific debates have addressed the role of ethnic origin and/or a specific genetic base for clozapine-induced agranulocytosis. Clozapine is useful not only in patients with poor response (treatment resistance being the main indication), but also in controlling affective states and reducing extrapyramidal symptoms/tardive dyskinesia, violence and substance abuse – conditions that have been associated with increased suicide risk.

The potential decrease in suicide among schizophrenic patients treated with clozapine is estimated to be as high as 85% [1]. Using epidemiological methods to assess the overall mortality in current and former users of clozapine, it was found that the death index was lower during current clozapine use than during periods of non-use. Mortality from suicide was also decreased among current clozapine users by comparison with past users [2]. Patients taking clozapine undergo weekly monitoring with health professionals, a procedure that provides additional benefits of both surveillance and management.

The most serious and potentially fatal side effect of clozapine is agranulocytosis, which develops in 1–2% of all schizophrenic patients treated with clozapine. It was indicated that genetic factors marked by major histocompatibility complex haplotypes (HLA-B38, DR4, DQw3) may be associated with the susceptibility of Jewish schizophrenic patients treated with clozapine to develop agranulocytosis [3,4]. The estimated incidence of these haplotypes in the Jewish population of the United States and Israel is less than 5% (E. Gazit, personal communication, 1999). Only some of them (the real incidence is unclear) develop agranulocytosis or granulopenia under clozapine treatment [5]. Pfister et al. [6] found the same haplotype in the only Native Americans examined and explain it on the basis of the common HLA-B16 allele (characteral subvariant B38 for Jews and subvariant B39 for native Americans without Jewish descent).

Concerning proposed groups at high risk, Pisciotta et al. [7] found that clozapine-induced agranulocytosis is predominant in a young subset and similarly affects both sexes. Based on a large European sample, Claas and team [8] concluded, "neither gene products of the HLA system nor the known granulocyte-specific antigens are predictive of agranulocytosis or granulopenia." This amendment was supported by appropriate statistical analytical assessment [9]. A recent study did not find a significant difference in ethnic origin between the agranulocytosis and non-agranulocytosis groups of Israeli Jewish patients [10]. Most recently, Meged and co-workers [11] confirmed that the incidence of agranulocytosis in clozapine-treated patients is similar between Jews and non-Jews. Thus, till now, many current investigations are devoted to the identification of such subsets of population (not only Jewish) and to determining "responsible" serotypes.

Recently, based on a small Israeli sample (including Ashkenazi as well Sephardic Jews) of schizophrenics who developed agranulocytosis or granulopenia under clozapine treatment, Amar and colleagues [12] discovered a common HLA haplotype DQB1*0201. They did not find the previously reported [3,4] association of DRB1*0402-DQB1*0302-DQA1*0301 HLA haplotype and increased susceptibility for clozapine-induced agranulocytosis in Jewish patients. It was also emphasized that the B38 antigen, otherwise widespread in the Jewish population, was not present in the examined cohort. It was proposed that susceptibility for clozapine-induced agranulocytosis could be encoded "either DQB1*0201 or tightly linked gene nearby" [12].

Moreover, in the recent study of Corzo et al. [13] it was found that a dominant gene (or genes?) within the MHC region (marked by HSP70-1 and HSP70-2), but not necessarily HLA haplotypes as was proposed previously, is associated with clozapine-induced agranulocytosis in different ethnic groups. In addition, the possibility of the existence of a second gene, in linkage disequilibrium with the HLA system and responsible for the occurrence of agranulocytosis, cannot be excluded at this time [14]. Most remarkable is the recent discovery of the linkage between susceptibility to the condition and a high frequency of the tumor necrosis factor b4 and d3 microsatellite alleles in two different ethnic (Jewish and non-Jewish origin) groups, whereas "protection" against clozapine-induced agranulocytosis was associated with the microsatellite b5 [15]. This is consistent with the hypothesis that susceptibility to such drug-induced reaction is partly due to the linkage disequi-

MHC = major histocompatibility complex

librium of these alleles with HLA-B and DR specificities [3,4].

It was noted that "clozapine is not particularly toxic in Jewish patients, but the subpopulation of individuals expressing this phenotype is at increased risk of neutropenia" [16]. Thus, no definitive inherited condition or other specific risk factors can predict emergence of clozapine-induced agranulocytosis or granulopenia, even in a Jewish population [17], and some hypotheses were proposed to explain the association between HLA and agranulocytosis [10]. Therefore, since the HLA typing is not performed as a routine procedure (at least in clinical practice in Israel), Ashkenazi Jewish origin itself should not be considered as a risk factor warranting avoidance of clozapine in such patients, which was proposed by some authors [18].

An attempt to help protect patients from developing potentially fatal agranulocytosis secondary to treatment with clozapine was the establishment in the USA of the Clozaril National Registry in 1989. This system fostered early detection of white blood cell suppression, prevented retreatment with clozapine of patients who had previously developed WBC suppression, and resulted in lower than expected rates of agranulocytosis and associated deaths [19]. During a 5 year period the use of clozapine in 99,502 American patients was associated with a total of 382 cases of agranulocytosis (0.38%) versus an expected cumulative total of 995 cases (based on the pre-Registry rate of 1–2%) [20]. Based on the expected agranulocytosis rate, up to 149 deaths might have been anticipated; instead, there were only 12 deaths attributed to complications of agranulocytosis [20]. Use of clozapine in Israel is also linked to mandatory WBC testing and has been associated with 15 proven cases of agranulocytosis (less then 1%) [11]. Establishing such a registry in Israel could serve as an early warning system to promote the safe and effective use of clozapine. This registry would increase patient compliance and treatment implementation efficiency, substantially reducing potential fatal outcomes. Thus, a registry database that contains information on the WBC, exact haplo- and genotype, and demographics of every Israeli patient who has received the medicine could serve as a unique epidemiological and research resource, as well as an early warning system.

Widespread use of clozapine has been hindered by fear of agranulocytosis and associated deaths. The treatment with clozapine is cost effective, and the significant decrease in the risk of suicide far outweighs the very low risk of mortality from agranulocytosis.

WBC = white blood cell

References

1. Meltzer HY. Suicide in schizophrenia: risk factors and clozapine treatment *J Clin Psychiatry* 1998;59(Suppl 3):15–20.
2. Walker AM, Lanza LL, Arellano F, Rothman KJ. Mortality in current and former users of clozapine. *Epidemiology* 1997;8:671–7.
3. Lieberman JA, Yunis J, Egea E, Canoso RT. HLA-B38, DR4, DQw3 and clozapine-induced agranulocytosis in Jewish patients with schizophrenia. *Arch Gen Psychiatry* 1990;47:945–8.
4. Yunis JJ, Corzo D, Salazar M, Lieberman JA, Howard A, Yunis EJ. HLA associations in clozapine-induced agranulocytosis. *Blood* 1995;86:1177–83.
5. Yunis JJ, Lieberman JA, Yunis EJ. The major histocompatibility complex association with clozapine-induced agranulocytosis. The USA Experience. *Drug Saf* 1992;7(Suppl 1):7–9.
6. Pfister GM, Hanson DR, Roerig JL, Landbloom R, Popkin MK. Clozapine-induced agranulocytosis in a Native American: HLA typing and further support for an immune-mediated mechanism. *J Clin Psychiatry* 1992;53:242–4.
7. Pisciotta AV, Konings SA, Ciesemier LL, Cronkite CE, Lieberman JA. On the possible mechanisms and predictability of clozapine-induced agranulocytosis. *Drug Saf* 1992;7(Suppl 1):33–44.
8. Claas FH, Abbott PA, Witvliet MD D'Amaro J, Barnes PM, Krupp P. No direct clinical relevance of human leucocyte antigen (HLA) system in clozapine-induced agranulocytosis. *Drug Saf* 1992;7(Suppl 1):3–6.
9. Abt K, Gulich A, Krupp P, Reinberg W. HLA-associations in Clozapine (Leponex(r))-induced granulocytopenia and agranulocytosis. Statistical viewpoints. *Drug Saf* 1992;7(Suppl 1):10–16.
10. Valevski A, Klein T, Gazit E, Meged S, Stein D, Elizur A, Narinsky ER, Kutzuk D, Weizman A. HLA-B38 and clozapine-induced agranulocytosis in Israeli Jewish schizophrenic patients. *Eur J Immunogenet* 1998;2511–13.
11. Meged S, Stein D, Sirota P, Melamed Y, Elizur A, Shmuelian I, Gazit E. Human leukocyte antigen typing, response to neuroleptics, and clozapine-induced agranulocytosis in Jewish Israeli schizophrenic patients. *Int Clin Psychopharmacol* 1999;14:305–12.
12. Amar A, Segman R, Strussberg S, Sherman L, Safriman C, Lerer B, Brautbar C. An association of clozapine-induced agranulocytosis in schizophrenics and HLA-DQB1*0201. *Int J Neuropsychopharmacol* 1998;1:41–4.
13. Corzo D, Yunis JJ, Salazar M, Lieberman JA, Howard A, Awdeh Z, Alper CA, Yunis EJ. The major histocompatibility coregion marked by HSP70-1 and HSP70-2 variants is associated with clozapine-induced agranulocytosis in two different ethnic groups. *Blood* 1995;86:3835–40.
14. Corzo D, Yunis JJ, Yunis EJ, Howard A, Lieberman JA. HSP70-2 9.0 kb variant is in linkage disequilibrium with the HLA-B and DRB1* alleles associated with clozapine-induced agranulocytosis. *J Clin Psychiatry* 1994;55(Suppl B):149–52.
15. Turbay D, Lieberman J, Alper CA, Delgado JC, Corzo D, Yunis JJ, Yunis EJ. Tumor necrosis factor constellation polymorphism and clozapine-induced agranulocytosis in two different ethnic groups. *Blood* 1997;89:416–74.
16. Lieberman JA, Alvir JM. A report of clozapine-induced agranulocytosis in the United States. Incidence and risk factors. *Drug Saf* 1992;7(Suppl 1):1–2.
17. Valevski A, Modai I, Weizman A. Clozapine-induced agranulocytosis [Review]. *Harefuah* 1994;126:32–5 (Hebrew).
18. Koren W, Kreis Y, Duchowiczny K, Prince T, Sancovici S, Sidi Y, Gur H. Lactic acidosis and fatal myocardial failure due to clozapine. *Ann Pharmacother* 1997;31:168–70.
19. Honigfeld G. Effects of the clozapine national registry system on incidence of deaths related to agranulocytosis. *Psychiatr Serv* 1996;47:52–6.
20. Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry* 1998;59(Suppl 3):3–7.

Correspondence: Dr. I. Reznik, Ness-Ziona Mental Health Center, P.O.Box 1, Ness-Ziona 74100, Israel. Phone: (972-8) 938-4125, Fax: (972-8) 938-4127, email: ilyarez@netvision.net.il