



Agranulocytosis in clozapine: myths and facts

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Ladies and gentlemen, good afternoon!

Let me talk to you about myths and facts of clozapine. Of course you are all aware of the fact that clozapine has unique efficacy in therapy refractory schizophrenia, and you may know also that it has unique effects in co-morbid suicidality, aggressiveness and substance abuse.

Today I will focus on agranulocytosis which is of course a specific risk of clozapine and caused its bad reputation of a dangerous drug.

Statement of Potential Conflicts of Interest

Agranulocytosis in clozapine: myths and facts

Relating to this presentation, there are no relationships that could be perceived as potential conflict of interests.

Outline



- History and some facts
- Mortality in clozapine users
- Appraisal of WBC results
- Rechallenge after leukopenia
- Termination of WBC controls
- For all remaining questions:
Dutch Clozapine Guideline (in English) at:
www.clozapinepluswerkgroep.nl

Here is the outline of my talk: I will touch on the history of clozapine and mortality in its users.

I will give some information on the appraisal of white blood cell (WBC) results and rechallenge after leukopenia.

And finally I will talk about the termination of WBC controls.

Agranulocytosis: history and facts

- Incidence of agranulocytosis in Europe before mandatory WBC controls: **1 to 2% per year**[#]
- Incidence of agranulocytosis in clinical research for registration in the US (1989): **1.3% in the first year***
- Mortality of agranulocytosis before 1989: **32%*** (now 3-4%)
- Mortality in unexpected agranulocytosis: 16%
- Mortality caused by clozapine agranulocytosis (with controls): 1:10.000 (US) en 1:26.000 (GB)

Honigfeld, et. al.(1998). J Clin Psychiatry;59 Suppl 3:3-7,

*United States package insert

Before the introduction of mandatory white blood cell counts the incidence of agranulocytosis in clozapine users in Europe was 1-2% per year. In the US it was 1.3% in the first treatment year.

The mortality in agranulocytosis before 1989 was 32%, nowadays it is 3-4%. In unexpected agranulocytosis in the general population mortality may be as high as 16%, but better care has often reduced it to 5%.

Nowadays the overall mortality caused by clozapine agranulocytosis (with mandatory WBC controls) lies between 1 in 10,000 clozapine users in the US and 1 in 26,000 in Great Britain and Ireland: it is extremely low.

So, is clozapine a dangerous drug? I do not think so.

May be that you know of other lethal risks like myocarditis of diabetes which may cause myocardial infraction.

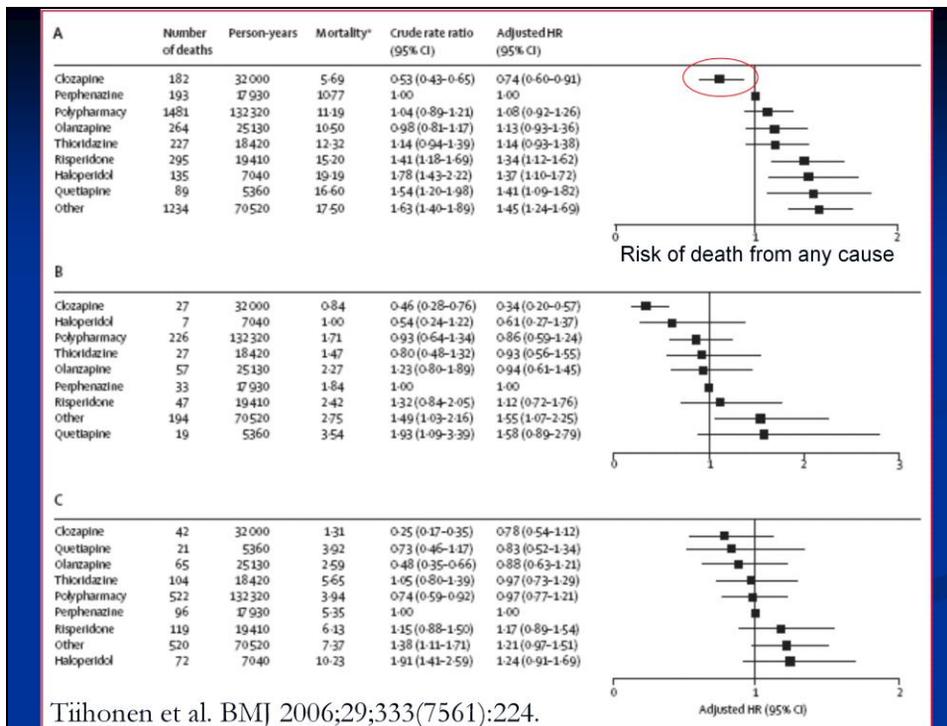
Let's see whether clozapine carries a larger risk than other antipsychotics.

Mortality in current clozapine users vs. past clozapine users

- 67,072 current and former clozapine users
- 85,399 person-years
- Lower mortality in current users
- Suicides per year: 0.039% vs. 0.219% (RR 5.67)

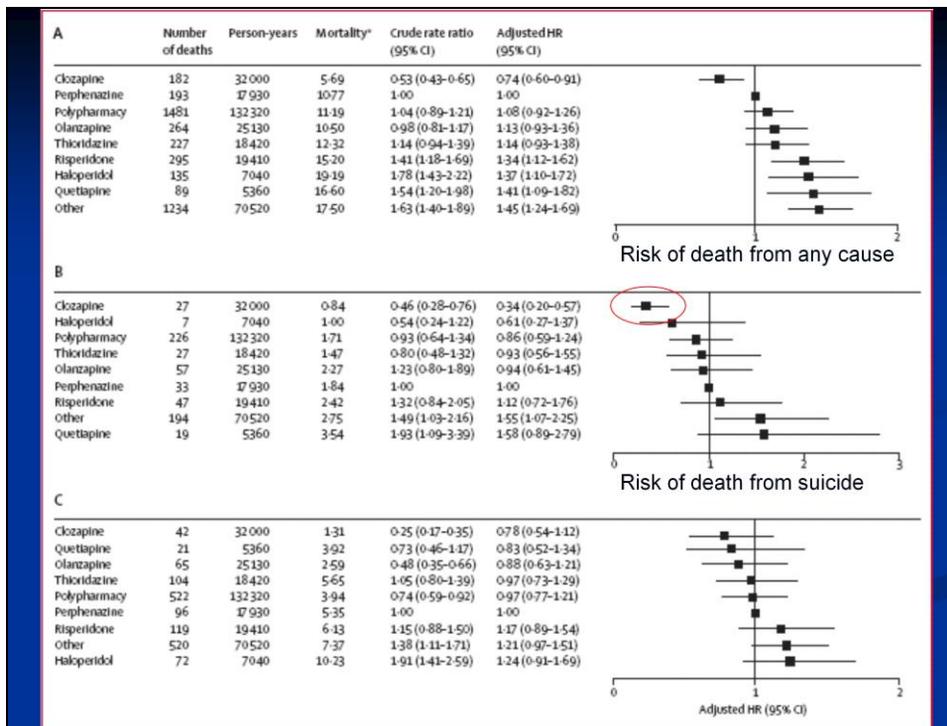
Walker et al. *Epidemiology* 1997;8:671-7.

Nearly 20 years ago Walker and colleagues analysed data of more than 60,000 current and former clozapine users of the Clozaril National Registry for US patients, more than 85,000 patient years. He found a lower mortality in current clozapine users than in former users, which was mainly driven by a fivefold reduction of suicides.

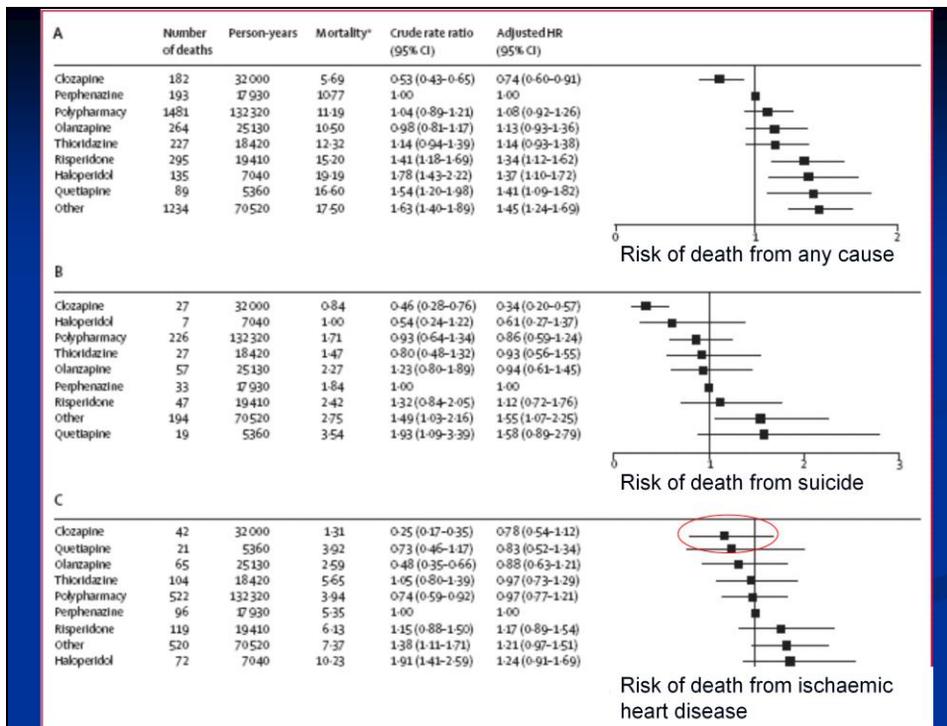


Here I show you the results of the famous Tiihonen Fin 11 study, where he analysed all people in Finland who were hospitalized for the first time for schizophrenia or schizoaffective disorder in the period of 1997 to 2004 and combined their data with prescription data and death certificates.

And here you see the results: the overall mortality was lowest for clozapine users.



Again, risk of death for suicide was lowest in clozapine users. You may be afraid that clozapine users got more diabetes and died from ischaemic heart disease.



This proved to be untrue. Again in clozapine users the risk was the lowest. You may object that this is a result of laboratory controls or frequent patient-staff contact.

Possible confounders

- 14,754 individuals with SMI
- 879 deaths
- mortality clozapine vs. non-clozapine after adjustment: hazard ratio 0.4 (95% CI 0.2-0.7)
- mortality clozapine vs. olanzapine after adjustment: hazard ratio 0.4 (95% CI 0.2-0.8)
- True for natural and unnatural causes of death

Hayes et al. Schiz Bull 2014, in press

A recent study by Hayes and colleagues looked into this question. They had access to the electronic mental health records of nearly 15,000 individuals with serious mental illness from 2007 to 2011 and observed 879 deaths.

The mortality in clozapine users vs. non-clozapine users appeared to be 60% lower, even when adjusted for a range of possible confounders. The result remained unchanged when comparing clozapine- to olanzapine-users.

And the investigators showed that not only the risk for unnatural cause of death (for example suicide) was lower, but also the risk for natural causes of death.

So my conclusion is that clozapine is the safest of all antipsychotics in people who are indicated for it.

Types of low WBC counts

- Measurement or reporting error
- Circadian rhythm
- Benign ethnic neutropenia
- Benign clozapine leukopenia (transient peripheral destruction; Hummer et al. 1992: 8/68 patients)
- malignant leukopenia leading to agranulocytosis

Let me come to practical aspects of clozapine. What does a low WBC count mean?

First of all it may be a measurement or reporting error. A second reason may be circadian rhythm. Some people do have abnormal low leukocytes in the morning and normal values in the late afternoon.

In both cases it is appropriate to repeat the WBC count the same day in the late afternoon and evaluate the result immediately. If it is normal, clozapine should not be stopped.

Another possible cause for low WBC is benign ethnic neutropenia, which is a normal variation and occurs especially in sub-Saharan Africans, but may occur in Caucasian families too.

Benign Ethnic Neutropenia (BEN)



	WBC		Neutrophils	
	BEN	Regular	BEN	Regular
Normal (green)	$> 3,0 \times 10^9$	$> 3,5 \times 10^9$	$> 1,5 \times 10^9$	$> 2,0 \times 10^9$
Lowered (amber)	$2,5 - 3,0 \times 10^9$	$3,0-3,5 \times 10^9$	$1,0-1,5 \times 10^9$	$1,5-2,0 \times 10^9$
Agranulocytosis (red)	$< 2,5 \times 10^9$	$< 3,0 \times 10^9$	$< 1,0 \times 10^9$	$< 1,5 \times 10^9$
Normal (green): satisfactory. Lowered (amber): continuation of clozapine with repeated measurement. Agranulocytosis (red): immediate cessation of clozapine.				

Rajagopal Postgrad Med J 2005

For Great Britain lower cut-offs for leukocytes and neutrophils in people with benign ethnic neutropenia have been published. The values are a half point (or 500) lower than the official values when to stop clozapine.

Let me come back to the other reasons for low WBC counts.

Types of low WBC counts

- Measurement error
- Circadian rhythm
- Benign ethnic neutropenia
- Benign clozapine leukopenia (transient peripheral destruction; Hummer et al. 1992: 8/68 patients)
- malignant leukopenia leading to agranulocytosis

Not all leukocyte counts where you have to cease clozapine administration lead to agranulocytosis. Some patients exhibit a benign form of clozapine leukopenia with transient peripheral destruction and normalization of leukocyte counts later on.

And of course: some patients do develop agranulocytosis if clozapine is not stopped immediately, or continue to agranulocytosis anyway. This is the malignant leukopenia we are afraid of.

Let me first come to the stages of neutropenia. I will touch on benign clozapine leukopenia later on.

Stages of neutropenia: risks and treatment

- $>1000/\mu\text{l}$: no significant risk of infection
- $500-1000/\mu\text{l}$: some risk of infection, treat fever like normal polyclinic patient
- $<500/\mu\text{l}$ (agranulocytosis): high risk of infection, nearly always clinical symptoms. Parenteral antibiotics.
- $<200/\mu\text{l}$: very high risk of (opportunistic) infections, reverse isolation, broad spectrum antibiotics

Here you see the risks and treatment in different neutrophil counts.

As long as they are above 1000, there is no risk of infection. Just stop clozapine and control WBC.

If the neutrophils fall between 500 and 1000 I personally consult a hematologist who will reassure me. There is some risk of infection, but fever may be managed like in a normal outpatient.

If the neutrophils are below 500 this is a real case of agranulocytosis with a high risk of infection and nearly all patients do have symptoms of infection, are hospitalized and treated with parenteral antibiotics. The mortality of this clozapine induced agranulocytosis is 3-4% nowadays.

If the neutrophils are lower than 200 reverse isolation is necessary.

Interruption/termination of treatment with clozapine

- EMA:
 - Leukocytes < 3000/ μ l and /or
 - Granulocytes < 1500/ μ l

- FDA:
 - Leukocytes < 3000/ μ l and/or
 - Granulocytes < 1500 / μ l

- Leukocytes < 2000/ μ l and/or
 - Granulocytes < 1000 / μ l

Let me come back to termination of clozapine treatment in low WBC. Interestingly the Food and Drug Administration (FDA) differs from the European Medicines Agency (EMA) on that point. While in Europe you must stop and may not rechallenge a clozapine patient if leukocytes fall below 3000 and/or granulocytes below 1500, in the US you just interrupt the treatment with clozapine and restart the patient on it when WBC has normalised.

Only if leukocytes were lower than 2000 and/or granulocytes lower than 1000 the patient may not be rechallenged. The American clozapine leaflet gives detailed information on how often and how long WBC must be controlled in case of restart of clozapine.

Nevertheless, there may be patients who were good clozapine responders but had to stop clozapine because of too low WBC.

Rechallenge

	failure
Leukopenia or granulopenia	38% (95% CI 26-52)
Agranulocytosis	1 of 1

- 17% of rechallenges after leukopenia/granulopenia develop agranulocytosis
- If mortality is set at 5% mortality of rechallenge (without earlier agranulocytosis) is 0.85%
- In the literature positive cases of rechallenge even after agranulocytosis

Dunk et al. Br J Psychiatry 2006;188:255-63.

Dunk and colleagues analysed all 53 cases of rechallenge in the UK and Ireland Clozapine Registry and found that the rechallenge failed because of blood dyscrasia in only 38% of earlier cases of leukopenia or granulopenia (judged upon European thresholds). This means that 62% were successful. 17% of these rechallenges developed agranulocytosis. If we combine this with a mortality of 5%, this off-label rechallenge carries a risk of death of less than 1%.

The single case of earlier agranulocytosis developed this again during rechallenge. Nevertheless I have found in the literature three successful rechallenges out of 4 cases with earlier agranulocytosis.

Rechallenge with Lithium

- All clozapine rechallenges with lithium in one hospital compared to rechallenges from the national clozapine register
- Lithium for 1 or 2 weeks on 0.4mmol/L, then start clozapine
- Failures 21.2% vs. 4%; ARD 29.8% (95% CI 14.6-45.0)
- Unclear whether Lithium really decreases the risk of agranulocytosis
- Advice: do not rechallenge patients with agranulocytosis or severe granulopenia >2 days during the first 18 weeks, except if other possible causes

Kanaan & Kerwin J Clin Psychiatry 2006 ;67:756-60.

It is well known that lithium increases WBC, probably by inducing granulocyte colony stimulating factor (GCSF). Kanaan & Kerwin studied 25 cases of rechallenge with lithium in their hospital and compared their results with those from the national clozapine registry where you may assume that no lithium was given.

They administered lithium one or two weeks before rechallenge, with a lithium level of 0.4 mmol/L and found only 4% failures in comparison to 21% in the national registry. So, clearly the patients on lithium had higher WBC and a lower risk of failure of rechallenge. Nevertheless it is unclear whether lithium really prevents agranulocytosis.

Kanaan & Kerwin advise not to rechallenge patients with earlier agranulocytosis or severe granulopenia for more than 2 days, except when other causes for low WBC are possible.

Rechallenge with Lithium

- All clozapine rechallenges with lithium in one hospital compared to rechallenges from the national clozapine register
- Lithium for 1 or 2 weeks on 0.4 mg/kg then start clozapine
- Failures 21.2% vs. 4% (RR 5.28% (95% CI 1.46-15.0))
- Unclear whether lithium really decreases the risk of agranulocytosis
- Do not rechallenge patients with clozapine if they have had a neutropenia or severe granulopenia >2 days during the first 18 weeks, except if other possible causes

Kanaan & Kerwin J Clin Psychiatry 2006;67:756-60.

To abstain from doing harm is part of the Hippocratic oath and reminds us that we should weigh the risk of harm of a medical intervention against its chance of benefit.

Most physicians would agree that cytostatics in cancer are a good choice, although some patients will die from the cytostatics.

The problem with clozapine is that it does carry certain risk (which may be overestimated) and has special efficacy (which is often undervalued).

Nevertheless a rechallenge in a patient who had to stop clozapine is a risky treatment with a mortality due to agranulocytosis of 0.85%. How should we weigh this mortality against more quality of life due to, for example, less threatening voices?

Here the concept of quality adjusted life years may help. You may ask your patient: how many months of the rest of your life would you give for less voices? Let's assume that the patient wants to give 3 months of the remaining 30 years of his life. Thus the patient wants to give 8.3% of his life while the risk of the rechallenge is only 0.85%, ten times lower.

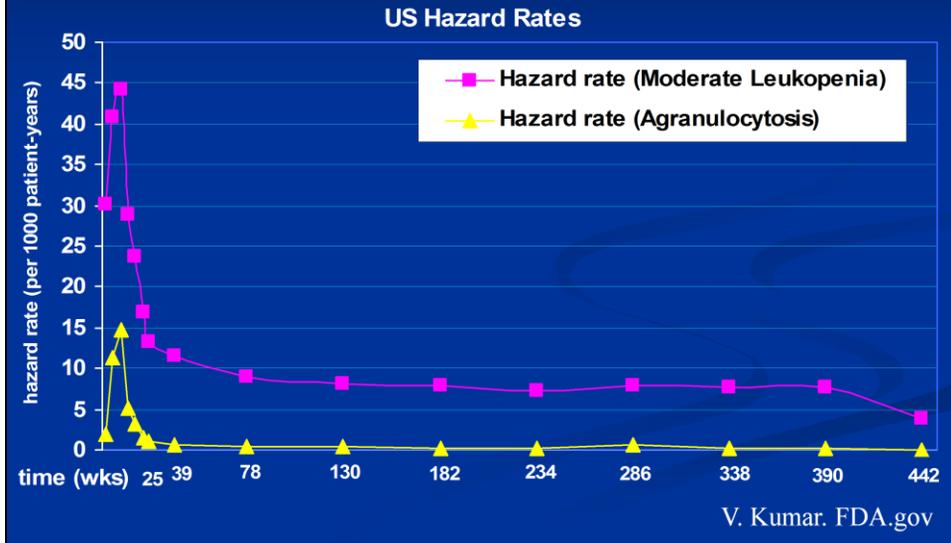
Of course we should explain the absolute risk of the rechallenge to the patient and his family, but the calculation may help ourselves to make up our mind.

Controls for ever and ever?

- EMA and FDA: monthly WBC counts up to four weeks after termination of treatment
- Patients want to stop

The last question I will touch on are the indefinite, perpetual monthly WBC counts, while patients urge us to stop the controls or even want to stop clozapine to avoid the blood drawings.

Risk of moderate leukopenia and agranulocytosis



Here you see the risk of moderate leukopenia and agranulocytosis from the clozapine registries. The risk is highest during the first 3 months and then steeply decreases. In the second half of year the risk decreases a little bit further and after the first year the risk is low, thou not absent.

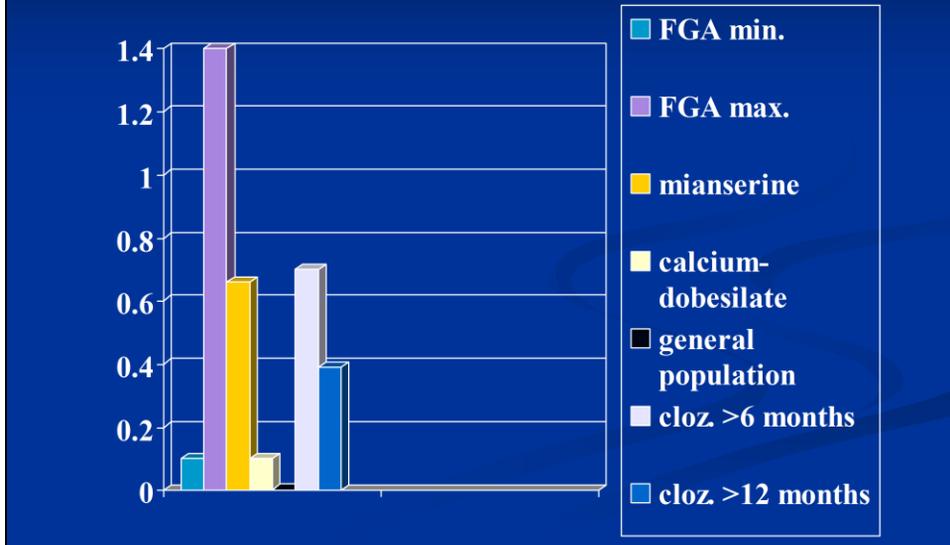
Incidence per 1000 patient years

Country	Severe leucopenia			Agranulocytosis		
	<18wks	19-52 wks	>52wks	<18wks	19-52 wks	>52wks
USA	6.93	0.48	0.45	6.76	0.40	0.39
GB/Ire	33.5	4.25	2.6	24.8	1.16	0.31
Australia	12.76	1.58	0.70	8.27	2.17	0.52

V. Kumar. FDA.gov

Here you see the absolute risks of leukopenia and agranulocytosis per 1000 patient years in different countries. Interestingly the risk varies: it is highest in Great Britain and Ireland and lowest in the US. (More recent cohorts in these countries show even more favorable figures, data not shown).

Agranulocytosis per 1000 person years



Here you see the risk in perspective: the two bars to the left show the lowest and highest risk I have found in the literature on agranulocytosis in first generation antipsychotics. The yellow bar is the risk of agranulocytosis in mianserin and to the right you see the risk of agranulocytosis in clozapine after the first treatment year (based on the recent cohorts).

If we calculate (based on the former cohorts) that all causes of severe neutropenia develop agranulocytosis the value varies between 0.84 per 1000 patient years in the US and 2.9 in Great Britain and Ireland, which still is only double the maximum risk of FGA's, where we never control leukocytes and certainly not every month.



Here I show you the calculated mortality if we stop with WBC controls after the first treatment year (based on the former cohorts).

I have multiplied the combined risk of severe leukopenia and agranulocytosis with a mortality of 16%. Then, in the US the mortality of stopping WBC controls is 0.13 and in Great Britain and Ireland 0.46 in 1000 patient years.

If we take a mortality of 3% or 4% and/or assume that only half of the cases with severe leukopenia develop agranulocytosis the figures would be much lower.



Here I show you the reduction of mortality due to suicide if the patient is treated with clozapine. You may notice that the risk difference is greater than the risk of death by agranulocytosis because of stopping the controls. Put into other words: if the patient stops with clozapine the mortality due to suicide is higher than when he continues clozapine without WBC counts and accepts a low risk of death due to agranulocytosis. (Remember: First, do no harm!).



And here these figures are put into the perspective of mortality of the general Dutch population: the bar to the left is mortality due to home or leisure accidents, the middle bar mortality due to an occupational accident and the bar to the right represents mortality to a traffic accident.

These risk may help to explain the risk of stopping with WBC controls to the patient and his family: “the magnitude of risk is comparable to the risk of dying from an accident at home or by traffic”.

Conclusion

- Mortality GB and US resp. caused by termination of WBC controls after the 1st year: 0.46/1000 and 0.13/1000 patient-years
- If mortality of agranulocytosis is set at 5% and not 16% the risk is 0.15 and 0.04/1000 patient-years
- In the second 6 months of clozapine treatment these risks are about twice as high.

Schulte, Ann Pharmacother 2006;40:683-688

My conclusion is that if we stop the WBC controls after the first treatment year of clozapine, the mortality due to htis is 0.46 per 1000 patient years in GB and Ireland and 0.13 in the US. These figures are even lower if we assume a mortality in clozapine agranulocytosis of 5% and/or that many cases of severe leukopenia do not progress to agranulocytosis.

In the second half of year of clozapine treatment these risks are about twice as high.

This is the reason why the Dutch Clozapine Collaboration Group in its guideline has taken the following position:

Dutch clozapine guideline

- If a mentally competent and adequately informed patient explicitly wants to stop having routine blood tests, this can be permitted after the first six months of clozapine treatment.
- However, the WBC count must still be monitored immediately if there is any clinical suspicion of agranulocytosis.
- Low frequency tests, for example four times a year, are still advisable.



Clozapine
Medicine
of last resort

Do not overestimate
the risks

Clozapine is a medicine of last resort with unique efficacy. Do not overestimate the risks, but offer clozapine to your patients

Thank you for your attention!

For all remaining questions:
Dutch Clozapine Guideline (in English) at
www.clozapinepluswerkgroep.nl