Health Canada Santé Canada

The Impact of Guidelines and Recently Completed Studies on Clinical Trial Design (Oral Agents)

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The Issue:

- since the Diabetes Control and Complications Trial in 1993, several studies have shown that improved glucose control in Type 2 diabetes reduces the risk of mortality and macro- and micro-vascular disease
- since 1993 there has been a decrease in the target range for glucose control from a HbA1c of 9-10% to <7%

The Issue (2):

- in December 2003 the Canadian Diabetes Association published revised clinical practice guidelines with glycemic targets of HbA1c ≤ 7% or FPG = 4.0–7.0 mmol/L
- "the target HbA1c should be attainable within 6 to 12 months"
- HbA1c >9% is marked hyperglycemia and the recommended treatment is with 2 antihyperglycemic agents or insulin

The Issue (3):

- "several studies clearly show that even short-term exposure to hyperglycemia has significant impact on blood vessel walls. Aggressive treatment…can improve outcomes significantly."

The Problem:

- the revised CDA guidelines were not intended to apply to clinical trials, HOWEVER,
- under C.05.006 of the Food and Drug Regulations the Minister may refuse the sale of a drug for a clinical trial if (A) the use of the drug endangers the health of a clinical trial subject or other person, or (B) the clinical trial is contrary to the best interests of the clinical trial subject.

The Problem (2):

- the glycemic targets and withdrawal criteria for many clinical trials did not conform to the CDA guidelines
- maintaining subjects on inadequate glycemic control to “prove” efficacy or collect safety data may endanger the health of a clinical trial subject and is contrary to the best interests of the clinical trial subject

The Result:

- disagreements between reviewers and sponsors resulting in withdrawn submissions and delayed approvals of clinical trial applications

The Solution:

- proposed guidance

Type 2 Diabetes Clinical Trials:

- two primary types:
  - Phase II proof-of-concept
  - Phase III proof-of-efficacy and safety
- inclusion/exclusion criteria:
  - typically treatment naïve or poorly controlled diabetes with a HbA1c of 6.5–10.0%
  - reasonably healthy

Expectations for All Trials:

- subjects will receive:
  - adequate dietary and lifestyle counselling
  - adequate treatment for other conditions
    - recommended targets for patients with diabetes under current clinical practice guidelines:
      - hypertension: blood pressure <130/80 mm Hg
      - lipids: LDL-C <2.5 mmol/L **and**
        total cholesterol/HDL-C ratio <4.0

Expectations for All Trials (2):

- subjects should self-monitor blood glucose daily and self-monitor body weight at frequent intervals
- monitoring during the trial will conform to the CDA guidelines

Phase II trials:

- typically placebo-controlled proof-of-concept dose ranging studies
- 12-24 weeks duration with a 2+ week placebo run-in
- experimental drug is monotherapy or add-on to approved therapy
- objective is to demonstrate superiority to placebo and select dose(s) for phase III studies

Inclusion/Exclusion Criteria:

- HbA1c >9% should only be allowed when CDA target can be achieved in 6-12 months
  - target unlikely to be met in the placebo arm of a 24 week monotherapy, placebo-controlled trial
  - NOTE: EMEA suggests patients in placebo-controlled trials should have HbA1c <8.5% and patients with HbA1c of 8.5-10% should not be enrolled in trials >3 months duration

Withdrawal Criteria:

- primary risk is loss of glycemic control
- see physician if:
  - FPG >15 mmol/L on 2 consecutive days, >13.3 mmol/L on 3 consecutive days, or >12 mmol/L on 4 days per week (CDA CSS recommendation)
- withdraw if:
  - FPG laboratory values >15/15.5 mmol/L and no other explanation
  - symptomatic

Phase III trials:

- typically 1-2 years duration
- objective is to demonstrate efficacy and safety
- may evaluate a dose response
- efficacy:
  - non-inferiority or equivalence of one or more doses to an accepted treatment
  - usually apparent in <6 months

Inclusion/Exclusion Criteria:

- subjects should be representative of target patient population as per ICH guidelines
  - means higher HbA1c and more severe medical problems than would be allowed in phase II trials

Withdrawal Criteria:

- risks are loss of glycemic control (short-term) and lack of efficacy (long-term)
- short–term
  - withdrawal criteria should be similar to those for phase II trials

Withdrawal Criteria – long-term:

- after 3 months HbA1c should replace FPG as measure of blood glucose
- if HbA1c >7% at 6-12 months, dose escalation or addition of other therapies should be instituted
- at 52 weeks withdraw if HbA1c >8%
- progressive lowering of withdrawal limit towards HbA1c ≤ 7% by 104 weeks

Informed Consent:

- subjects should be informed that they could be maintained on a therapy that will delay optimal treatment

Issues/Considerations:

- pathogenesis of type 2 Diabetes involves 3 primary defects:
  - insulin resistance
  - insulin secretory dysfunction
  - hepatic glucose overproduction
- range from predominant insulin resistance with relative insulin deficiency to predominant secretory dysfunction with insulin resistance

Issues/Considerations (2):

- not all patients will respond adequately to a given regimen
  - monotherapy with currently effective antihyperglycemic agents lowers HbA1c by 1.0-1.5%
  - large variability in response (coefficient of variation ≥75%)

Issues/Considerations (3):

- GUIDE Trial (2004)
  - 27 week treatment
  - titrated to effective dose of gliclazide MR or glimepiride prior to treatment with upward dose adjustment of high dose of glimepiride at week 18 in non-responders
  - baseline HbA1c was 8.3 ± 1.1% (mean ± SD)
  - at week 9 HbA1c was 7.45 ± 1.1%

Issues/Considerations (4):

- ΔHbA1c over 27 weeks was ↓1.1 ± 1.1%
- means:
  - ≈15% of patients had an increase in HbA1c over the course of the trial
  - also ≈15% had decrease ≥ 2.2%

- upward dose adjustment with glimepiride at week 18 had no effect on HBA1c at week 27

Issues/Considerations (5):

- impact of withdrawal criteria
  - potential reduction in number of subjects completing trial (only 50% may meet CDA target)
  - statistical considerations
    - effect on variance and sample size calculations
    - use of LOCF?
    - survival analysis as a 2nd endpoint?

Issues/Considerations (6):

- increased risk of hypoglycemia with more aggressive treatment
- new agents better????

Issues/Considerations (7):

- "real-world" trials
  - inclusion of subjects with HbA1c >10%
  - inclusion of patients with dyslipidemia and cardiovascular problems
  - special populations (elderly, paediatric, etc.)
  - 3 agent combination therapy in difficult to treat subjects

Issues/Considerations (8):

- there is a difference between trials to evaluate therapeutic outcomes and those to evaluate efficacy of new drugs
- clinical trials designed to test the efficacy of a new drug are not real world - they are experiments
  - experiments should build on prior knowledge

Issues/Considerations (9):

- in the real world many patients may not meet targets, BUT
- in the real world, physicians can also adjust therapy at any time
- in a clinical trial options for dose adjustments or addition of new therapies are limited by the protocol
  - only options may be protocol violation or withdrawal

Issues/Considerations (10):

- knowingly maintaining subjects on suboptimal therapy is a violation of the Declaration of Helsinki and ICH
- “The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over the interests of science and society.” (ICH GCP Article 2.3)

Issues/Considerations (11):

- the goal is to allow a scientifically valid assessment of the efficacy and safety of a therapeutic product while ensuring that the safety of subjects is not compromised

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