

## Journal Scan

### **Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial**

This was a multicentre, double-blind, randomised, placebo-controlled trial at nine centres in Japan. Patients aged 2 years or more experiencing a relapse of frequently relapsing nephrotic syndrome (FRNS) or steroid dependant nephrotic syndrome (SDNS) were recruited. Patients were randomly assigned to receive rituximab (375 mg/m<sup>2</sup>) or placebo once weekly for 4 weeks. All patients received standard steroid treatment for the relapse at screening and stopped taking immunosuppressive agents by 169 days after randomisation. Patients were followed up for 1 year.

Of 52 patients who underwent randomisation, 48 received the assigned intervention (24 were given rituximab and 24 placebo). The median relapse-free period was significantly longer in the rituximab group (267 days, 95% CI 223-374) than in the placebo group (101 days, 70-155; hazard ratio: 0.27, 0.14-0.53;  $p < 0.0001$ ). Ten patients (42%) in the rituximab group and six (25%) in the placebo group had at least one serious adverse event ( $p = 0.36$ ).

#### **Comment**

Nephrotic syndrome is the most common glomerular disease in pediatric practice. While most cases are due to minimal change disease and are responsive to steroids, upto 50% of these children go on to develop FRNS or SDNS. This increases their overall exposure to glucocorticoids leading on to long term consequences of steroid therapy in childhood, including short stature and low bone mass. The present study shows that a longer period of remission can be achieved with use of the B lymphocyte depleting monoclonal antibody rituximab, allowing the children more time to recover from the side effects of steroids.

*Iijima K, Sako M, Nozu K, Mori R, Tachida N, Kamei K, Miura K, Aya K, Nakanishi K, Ohtomo Y, Takahashi S, Tanaka R, Kaito H, Nakamura H, Ishikura K, Ito S, Ohashi Y; Rituximab for Childhood-onset Refractory Nephrotic Syndrome (RCRNS) Study Group. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2014 ;384:1273-81.*

### **Glycemic control and excess mortality in type 1 diabetes**

This study recruited 33915 patients from the Swedish type 1 diabetes registry from 1998 onwards and followed them up until 2011 to assess their mortality and compared with that of controls matched for age sex and county of residence. During follow-up 8% of the patients died, compared to 2.9% of the controls (adjusted hazard ratio 3.52). Death due to cardiovascular causes occurred in 2.7% and 0.9% of patients and controls respectively (adjusted hazard ratio 4.6).

Further the adjusted hazard ratios compared to controls for all cause mortality as well as cardiovascular event related mortality rose with rising glycated hemoglobin (HbA1c) i.e with worsening glycemic control. Adjusted hazard ratio for all cause mortality among patients compared to controls rose from 2.36 for patients with HbA1c  $\leq 6.9\%$  to 8.51 for HbA1c  $> 9.7\%$ . Likewise adjusted hazard ratios compared to controls for deaths from cardiovascular causes rose from 2.92 to 10.46 when comparing patients with HbA1c  $\leq 6.9\%$  with those having HbA1c  $> 9.7\%$ .



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### Comment

While it is well known that type 2 diabetes is associated with excess death, and more particularly cardiovascular disease related death compared to the general population, this study conclusively extends this fact to type 1 diabetes as well. The strength of the study is that, by using the type 1 diabetes registry of Sweden, almost all the patients with type 1 diabetes living in Sweden during the study period were included in the study, giving a very large population base to this study.

The authors also demonstrated the adverse impact of poor glycemic control on mortality. However reduction in mortality through tight glycemic control has been difficult to demonstrate in prospective randomized trials including the Diabetes Control and Complications Trial (DCCT) due to the small number of deaths occurring in the relatively young population of type 1 diabetes mellitus. However in the 10 year follow-up data of the original cohorts involved in the DCCT trial, a difference in mortality between the tight glycemic control arms and the conventional arms did emerge. Thus reducing mortality could be an additional rationale for good glycemic control in patients with type 1 diabetes.

*Lind M, Svensson AM, Kosiborod M, Gudbjörnsdottir S, Pivodic A, Wedel H, Dahlqvist S, Clements M, Rosengren A. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med 2014;371:1972-82.*

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### Risk of upper gastrointestinal bleeding from different drug combinations

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This is an analysis of data from 114,835 patients with upper gastrointestinal bleed (930,888 person-years of follow-up) identified from 7 population-based health care databases. Drug exposure was determined based on prescriptions of non selective NSAIDs, COX-2 inhibitors, or low-dose aspirin, alone and in combination with other drugs that increase the risk of upper gastrointestinal bleed (UGIB). Authors measured relative risk (incidence rate ratio [IRR] during drug exposure vs nonexposure) and excess risk due to concomitant drug exposure (relative excess risk due to interaction [RERI]).

Monotherapy with non selective NSAIDs increased the risk of diagnosis of UGIB (IRR, 4.3) to a greater extent than monotherapy with COX-2 inhibitors (IRR, 2.9) or low-dose aspirin (IRR, 3.1). Combination therapy generally increased the risk of UGIB; concomitant non selective NSAID and corticosteroid therapies increased the IRR to the greatest extent (12.8) and also produced the greatest excess risk (RERI, 5.5). Concomitant use of non selective NSAIDs and aldosterone antagonists produced an IRR for UGIB of 11.0 (RERI, 4.5). Excess risk from concomitant use of non selective NSAIDs with selective serotonin reuptake inhibitors (SSRIs) was 1.6, whereas that from use of COX-2 inhibitors with SSRIs was 1.9 and that for use of low-dose aspirin with SSRIs was 0.5. Excess risk of concomitant use of non selective NSAIDs with anticoagulants was 2.4, of COX-2 inhibitors with anticoagulants was 0.1, and of low-dose aspirin with anticoagulants was 1.9.

### Comment

This study demonstrates the importance of rational drug use and thorough knowledge of drug interactions when practicing medicine safely. Drugs should be used only if indicated and the benefits outweigh the risk. Even drugs widely considered to be free from UGIB risk such as COX-2 inhibitors and low dose aspirin were found to increase the incidence of UGIB. Particularly risky in terms of UGIB are combinations of NSAIDs with glucocorticoids and aldosterone antagonist (spironolactone). Review of drug history should form a routine part of evaluation of a patient of UGIB.

*Masclee GM, Valkhoff VE, Coloma PM, de Ridder M, Romio S, Schuemie MJ, Herings R, Gini R, Mazzaglia G, Picelli G, Scotti L, Pedersen L, Kuipers EJ, van der Lei J, Sturkenboom MC. Risk of upper gastrointestinal bleeding from different drug combinations. Gastroenterology 2014;147:784-792.*

### Reviewers

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