Pioglitazone for advanced fibrosis in NASH: New evidence, new challenges

UNIVERSITÀ DEGLI STUDI DI TORINO

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Giovanni Musso[1]M.D., Maurizio Cassader[2] Ph.D., Elena Paschetta[1]M.D, Roberto Gambino[2] Ph.D.

[1]*Gradenigo Hospital, Italy*
[2]*Department of Medical Sciences, University of Turin, Italy*

Corresponding author:

Giovanni Musso

Gradenigo Hospital, Turin

C.[so] R. Margherita 8

10132 Turin, Italy

Phone: +39-11-8151283

E-mail: giovanni_musso@yahoo.it

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Maurizio Cassader: conducted research, analyzed and discussed data, approved final version of the paper;

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Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al.. Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized, Controlled Trial. Ann Intern Med. 2016 Jun 21. doi: 10.7326/M15-1774.

Cusi et al randomized 101 diabetic/prediabetic patients with biopsy-proven NASH to pioglitazone 45 mg/d or placebo for 18 months. After the 18-month randomized controlled trial(RCT), patients underwent a control liver biopsy and non-responders on liver histology were enrolled in an open-label extension trial of pioglitazone 45 mg/d for additional 18 months, with a third liver biopsy at the end-of-treatment(EOT)(1). At the end of the 18-month RCT, pioglitazone treatment was associated with a higher percentage of NASH resolution and an improvement in mean fibrosis score. The additional 18 months of open-label treatment with pioglitazone were safe but did not improve liver histology further.

There is no established treatment for NASH, which is becoming the leading indication for liver transplantation(2). Promising agents in phase 2-3 of development induced NASH resolution and some ameliorated milder fibrosis stages(3,4), but none of them improved advanced (stage F3-4) fibrosis, the strongest predictor of a poor liver-related outcome in NAFLD(5). Hence, to fully understand what the RCT by Cusi et al. adds to current therapeutic approach to NASH, we must put this RCT into the context of available evidence for pioglitazone in NASH. We thus re-run our previous meta-analysis of RCTs in NASH(4) focusing on the impact of pioglitazone on advanced(stage F3-F4) fibrosis. A detailed description of search strategy, study selection, data extraction, synthesis and analysis is provided elsewhere(4) and in legend to Figure 1. We chose as main dichotomous outcome variable the improvement in advanced fibrosis, defined as (a)the number of NASH patients whose fibrosis stage changed from F3-F4 to F0-F2 at the EOT and as (b)the number of NASH patients with advanced (F3-F4) fibrosis whose fibrosis stage changed from F3-F4 to F0-F2 at the EOT. As secondary dichotomous outcome variables, we chose a $\geq$1 point improvement in fibrosis any-stage in NASH patients, and NASH resolution.

After adding the trial by Cusi(1), the analysis included 5 RCTs evaluating pioglitazone with post-treatment histology(392 participants, treatment duration ranging 6-24 months) .

Pooled results of RCTs showed that pioglitazone improved advanced fibrosis and fibrosis any-stage and induced NASH resolution (**Figure 1**). Statistical heterogeneity was low for all outcomes, suggesting a consistent drug effect size across studies.

Furthermore, after restricting the analysis to RCTs enrolling non-diabetic patients, pooled OR remained similar in magnitude and direction to overall effect: OR for improvement in advanced fibrosis in NASH: 3.99; 95%CI:1.23-12.97; I^2=0%, N=3, p=0.02; OR for improvement in fibrosis: 1.78; 95%CI:1.06-2.97; I^2=0%, N=3, p=0.02; OR for NASH resolution: 3.28; 95%CI:1.86-5.76; I^2=0%, N=3, p<0.0001. Therefore, the evidence for effectiveness of pioglitazone on liver disease in nondiabetic patients with NASH is at least as solid as for diabetic patients.

Thus, cumulative data analysis suggests pioglitazone has powerful anti-fibrotic properties.and has the potential to improve long-term prognosis of this group of the subgroup of NASH patients at higher risk of liver-related death. Nevertheless, the benefits of pioglitazone treatment should be weighed against the side effects of this drug, including weight gain, bone loss, edema and fluid retention, while recent evidence challenges the increased risk for bladder cancer(6).
Therefore a key issue in current clinical practice will be to develop strategies to optimize benefit/risk ratio of pioglitazone treatment in NASH and some clues may be grasped from existing literature:.

Pioglitazone seems a highly effective antifibrotic agent: if we calculate from Figure 1 panel B the number of patients with advanced fibrosis nedded to be treated to improve fibrosis in one patient (NNT), we find an NNT of 1.9 (i.e. two NASH patients with advanced fibrosis need to take pioglitazone to improve advanced fibrosis in one patient). Hence, it seems reasonable to restrict exposure to pioglitazone unwanted effects to those patients at higher liver-related risk, that is, those

with advanced fibrosis, since alternative, better tolerated therapeutic options were shown to be able to reverse NASH and milder fibrosis stages(3).

Second, it seems reasonable to limit the treatment duration and dose of pioglitazone to the strict necessacy to induce regression of advanced fibrosis and then to proceed with other therapeutic options to maintain histological response: within this context the trial by Cusi et al. suggests the use of pioglitazone beyond 18 months does not confer additional histological benefit(1). Dose adjustment has also been proposed, but it is unknown if doses lower than those used in NASH trials (ranging 30-45 mg/d) retain anti-fibrotic effects.

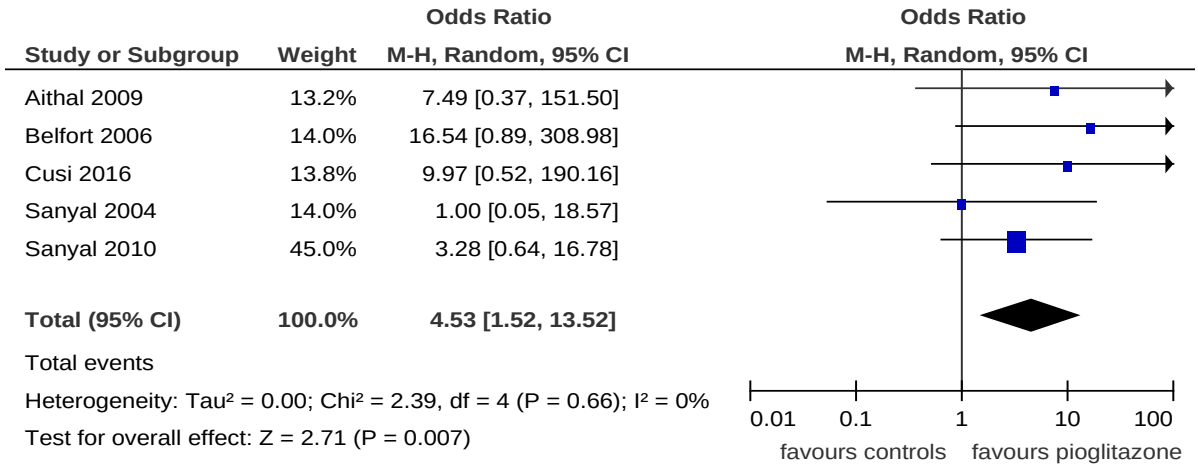
Finally, a careful individuation of patients who are more likely to respond to pioglitazone will be also help limit esposure to pioglitazone adverse effects: in the BALLET trial, baseline serum endotrophin levels identified pioglitazone responders and development of lower limb oedema: if confirmed by independent studies in NASH, this test may be used to select candidates for pioglitazone treatment in the future(7).

Implementing all these points in clinical practice and elucidating the therapeutic role of pioglitazone in nondiabetic NASH patients will be essential for an effective, individualized, patient-centered approach in the next future.

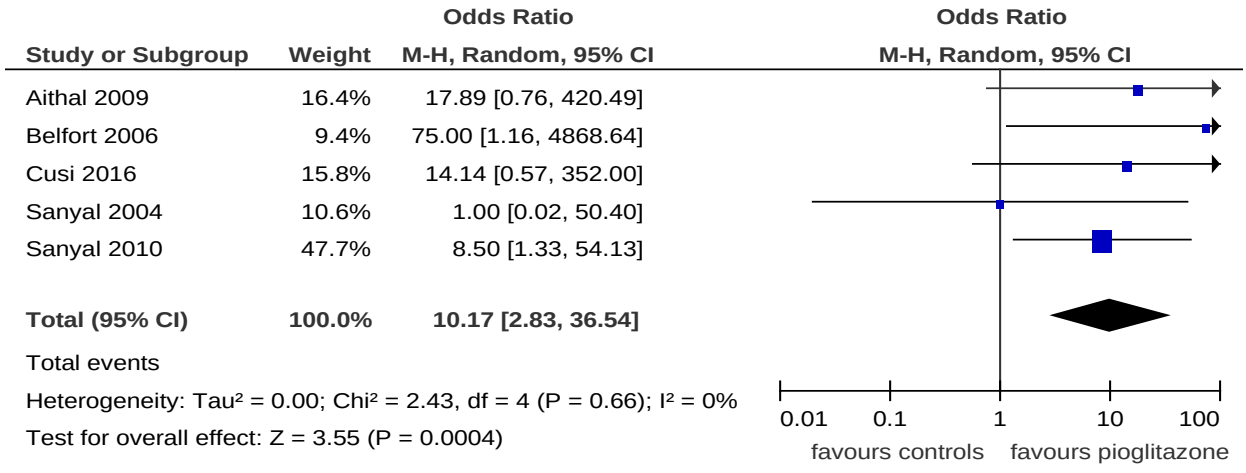
In the meantime, pharmacological research is developing compounds that keep the therapeutic effectiveness of pioglitazone but are devoid of its unwanted effects, including selective PPARγ modulators, mitochondrial target of thiazolidinediones (mTOT) modulators, stabilized R-enantiomer of pioglitazone DRX-065, and dual PPAR-α/γ agonists, some of which yielded promising results in preclinical/phase I-II clinical studies(8).

Figure 1

Panel A: OR for improvement in advanced (stage F3-F4) fibrosis in patients with biopsy-proven NASH, defined as the number of NASH patients whose fibrosis stage changed from F3-F4 to F0-F2 at the end-ot-treatment.



Panel B: OR for improvement in advanced (stage F3-F4) fibrosis in NASH patients with advanced fibrosis, defined as the number of NASH patients with advanced (F3-F4) fibrosis whose fibrosis stage changed from F3-F4 to F0-F2 at the end-of-treatment.

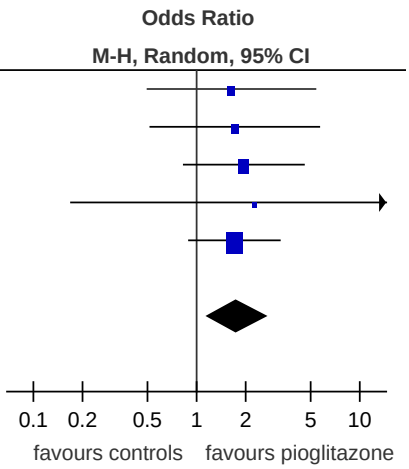


Panel C: OR for improvement by ≥1 stage in liver fibrosis (any stage) in NASH patients

Study or Subgroup	Weight	Odds Ratio M-H, Random, 95% CI
Aithal 2009	13.2%	1.64 [0.50, 5.35]
Belfort 2006	13.1%	1.71 [0.52, 5.64]
Cusi 2016	25.8%	1.95 [0.84, 4.54]
Sanyal 2004	2.8%	2.25 [0.17, 29.77]
Sanyal 2010	45.1%	1.71 [0.90, 3.24]
Total (95% CI)	**100.0%**	**1.77 [1.15, 2.72]**
Total events		

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 4 (P = 1.00); I² = 0%

Test for overall effect: Z = 2.60 (P = 0.009)



Panel D: OR for NASH resolution in all patients included in RCTs

Study or Subgroup	Weight	Odds Ratio M-H, Random, 95% CI
Aithal 2009	17.7%	2.26 [0.77, 6.63]
Belfort 2006	9.8%	4.40 [1.03, 18.74]
Cusi 2016	26.1%	4.44 [1.83, 10.78]
Sanyal 2004	3.5%	9.00 [0.81, 100.14]
Sanyal 2010	42.9%	3.51 [1.76, 7.01]
Total (95% CI)	**100.0%**	**3.65 [2.32, 5.74]**
Total events		

Heterogeneity: Tau² = 0.00; Chi² = 1.56, df = 4 (P = 0.82); I² = 0%

Test for overall effect: Z = 5.61 (P < 0.00001)

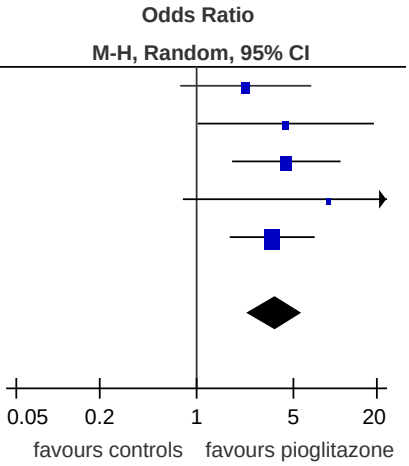


FIGURE 1 LEGEND

Figure 1

Panel A: Forest plot of RCTs showing the OR for improvement in advanced (stage F3-F4) fibrosis in patients with biopsy-proven NASH, defined as the number of NASH patients whose fibrosis stage changed from F3-F4 to F0-F2 at the end-ot-treatment.

Panel B: Forest plot of RCTs showing the OR for improvement in advanced (stage F3-F4) fibrosis in NASH patients with advanced fibrosis, defined as the number of NASH patients with advanced (F3-F4) fibrosis whose fibrosis stage changed from F3-F4 to F0-F2 at the end-of-treatment.

Panel C: Forest plot of RCTs showing the OR for improvement by ≥1 stage in liver fibrosis (any stage) in NASH patients

Panel D: Forest plot of RCTs showing the OR for NASH resolution in all patients included in RCTs

A full description of methods can be found in the previous article(4). Briefly, we re-run literature search including RCTs with post-treatment histology evaluating thiazolidinediones in NASH. Meta-analysis was performed according to the Cochrane Handbook of Systematic Reviews using RevMan Version 5.3.5 (Copenhagen: The Cochrane Collaboration 2008). Dichotomous outcome variables were presented as odds ratios (OR) with 95% CI. Fibrosis stage and NASH defined according to current guidelines(2).

We used the random-effect model, with significance set at P = 0.05. Statistical heterogeneity was assessed using the I^2 statistic: with I^2 values ≥50%, we planned to explore individual study characteristics and those of subgroups of the main body of evidence.

Sensitivity analysis was performed by removing 1 study at a time and repeating the meta-analysis to assess whether any one study significantly affected pooled estimates. Additionally, we planned *a*

priori subgroup analysis according to the following criteria: pioglitazone vs. rosiglitazone treatment, studies enrolling. non-diabetic vs. diabetic patients, treatment duration ≤1 year vs. >1 year, and for each item of the Cochrane Risk-of-Bias Tool.

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