Assessment of the Relative Effectiveness and Tolerability of Treatments of Type 2 Diabetes Mellitus: A Network Meta-analysis

Elias Zintzaras, PhD[1,2]; Michael Miligkos, MD, PhD[2]; Panayiotis Ziakas, MD, PhD[3]; Ethan M. Balk, MD[1]; Despoina Mademtzoglou, MSc[2]; Chrysoula Doxani, MD[2]; Theodoros Mprotsis, MSc[2]; Raman Gowri, MD[1]; Paraskevi Xanthopoulou, MD[2]; Ioanna Mpoulimari, MD[2]; Chrysoula Kokkali, MSc[2]; Georgia Dimoulou, MSc[2]; Paraskevi Rodopolou, PhD[2]; Ioannis Stefanidis, MD, PhD[2]; David M. Kent, MD[4]; and Georgios M. Hadjigeorgiou, MD, PhD[2,*]

[1]Center for Clinical Evidence Synthesis, The Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts; [2]Evidence-Based Medicine Unit, Department of Biomathematics, University of Thessaly School of Medicine, Larissa, Greece; [3]Division of Infectious Diseases, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, Rhode Island; and [4]Predictive Analytics and Comparative Effectiveness Center, The Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts

ABSTRACT

Purpose: The relative effectiveness and tolerability of treatments for type 2 diabetes mellitus (T2DM) is not well understood because few randomized, controlled trials (RCTs) have compared these treatments directly. The purpose of the present study was to evaluate the relative effectiveness and tolerability of treatments of T2DM.

Methods: We performed a network meta-analysis of available RCTs with pharmacologic interventions in T2DM and compared antidiabetic drugs and combination regimens with metformin (the reference drug). Glycemic control (proportion achieving HbA_{1c} goal) and tolerability (risk of hypoglycemia) were the primary outcomes of interest. Direct and indirect relative effects (unadjusted) were expressed as odds ratios and 95% CIs.

Findings: Eight treatments (glucagon-like peptide-1 [GLP-1] agonists plus metformin, sulfonylureas plus metformin, dipeptidyl peptidase-4 [DPP-4] inhibitors] plus metformin, colesevelan plus metformin, thiazolidinediones plus metformin, meglitinides plus metformin, α-glucosidase inhibitor plus metformin, and rosiglitazone monotherapy) outperformed metformin (direct effects). Triple combinations of GLP-1, thiazolinedione, insulin, metiglinide, or sulfonylureas added to a metformin backbone improved glycemic control (indirect effects). Higher risk of hypoglycemia was noted for sulfonylureas, α-glycosidases, and metiglinides when added to metformin (direct effects). Across indirect effects, only 17% of comparisons yielded less risk of hypoglycemia (70% were worse and 13% were comparable).

Implications: Our results point out the relative superiority of 2- and 3-drug combination regimens over metformin and summarize treatment effects and tolerability in a comprehensive manner, which adds to our knowledge regarding T2DM treatment options. (*Clin Ther*. 2014;36:1443–1453) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key Words: diabetes type 2, effectiveness, network meta-analysis, tolerability, treatment.

INTRODUCTION

The global burden of diabetes mellitus (DM) has increased from 153 million affected in 1980 to 347

Accepted for publication June 27, 2014.
http://dx.doi.org/10.1016/j.clinthera.2014.06.035
0149-2918/$ - see front matter

million affected in 2008. Type 2 DM (T2DM) is the main type of DM assumed to represent 90% of cases.[1,2] The mainstay of management consists of lifestyle modifications to increase physical activity and reduce weight[3] combined with pharmacologic interventions. Metformin has been the cornerstone of therapy for T2DM and remains the first-line option, unless contraindicated, across the leading T2DM guidelines.[4,5] However, as the effectiveness of metformin weakens with disease progression, the need for combination therapies becomes imperative. A relatively large number of drug classes and agents are available, but unlike metformin, there is no uniformity in the preferred scheme and time of initiation.[4–6] Moreover, the relative effectiveness and tolerability of newer drug classes are not well understood because few randomized, controlled trials (RCTs) have compared these treatments directly. Consequently, an integration of updated evidence regarding the relative effectiveness and tolerability of all available treatments is needed.

In that context, we systematically searched and catalogued the literature for all published RCTs in T2DM. We then performed a network of treatments meta-analysis[7] involving direct analysis (synthesis of RCTs with the same treatment comparisons), indirect analysis (comparison between treatments using an intermediate comparator), and combined analysis. We used metformin as the standard for comparison. The present methodology has already been applied in ranking the relative effectiveness of treatments in acute myeloid leukemia[8] and multiple sclerosis.[7,9]

METHODS

Search Strategy: Selection of RCTs

PubMed and Cochrane Central Register of Controlled Trials databases were searched (before January 2012) to identify all articles that investigated oral pharmacologic therapies in T2DM patients. The search criterion used combinations of the terms *diabetes mellitus*, *diabetes type 1*, *diabetes type 2*, *treatment*, and *therapy* with the following limits: *Randomized Controlled Trial*, *Humans*, English, and *All Adult*.

First the titles and thereafter the abstracts were retrieved and screened by 4 of the investigators (C.D., P.Z., I.M., and P.X.) independently to assess their appropriateness for inclusion in the network meta-analysis. After abstract screening, the articles were retrieved in full text to assess their eligibility for the analysis. Finally, all the reference lists of the eligible articles were extensively reviewed to identify additional published articles not indexed by PubMed and Cochrane databases.

Eligibility Criteria

RCTs that compared at least 1 oral agent (or combinations of drugs) over any other drug (or combination) in T2DM were considered eligible. The following studies were excluded: (1) cross-over studies that did not provide data for each period separately (only results for the first period were extracted), (2) follow-up and extension studies, (3) studies providing data based on post hoc or retrospective analysis, and (4) studies not providing adequate data to estimate effect sizes for the outcomes of interest. In articles involving data from different study periods of the same RCT, the results of the longest study period were considered. If there was inconsistency between articles of the same study (regarding period and cohort), the data of the initial article were extracted. For articles that examined >2 treatment arms, each of the pairwise comparisons was considered as a different study on the analysis level. To avoid inclusion of duplicate data that might lead to an overestimation of treatment effects, the retrieved studies were carefully appraised and examined by author names and affiliations, geographic location, and study period. In studies with overlapping data, the largest study was included in the analysis.

Data Extraction and Outcomes Definition

For each included study in the network meta-analysis, the following information was extracted: name of first author, year of publication, country of origin, sample size, treatments compared, ethnicity, sex, age, disease duration, obesity status, and intention-to-treat or per-protocol analysis (PP).

The relative effectiveness of the treatments was evaluated based on patients achieving the HbA_{1c} goal (ie, a binary response) defined by each study as the target HbA_{1c} for glycemic control; tolerability was evaluated based on patients having hypoglycemic episodes reported as adverse events in individual studies. For the outcome of patients achieving the HbA_{1c} goal, the definition of outcome was not consistent across the included studies. Seventy-seven percent of the included studies defined 7% as the