New algorithm ADA-EASD for treatment of hyperglycemia: novel aspects and critical points

Nuevo algoritmo ADA-EASD para el tratamiento de la hiperglucemia: aspectos novedosos y puntos críticos

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The diffusion on October 22nd 2008 about the new ADA-EASD algorithm for the treatment of T2D hyperglycemia,¹ that will be published in January 2009, simultaneously by Diabetes Care and Diabetología, did not cause, by different reasons, the same adherence among the experts in diabetes than the first algorithm published in August 2006.² As the authors recognize, one of the most important current limitations of the treatment algorithms for the T2D is the shortage of randomized and controlled studies, well designed, that compare different treatment strategies, particularly different combinations of drugs among them. However, the authors did not doubt to come to the “clinical criterion” to argue on some of the recommendations included in the document, in spite of the lack of solid scientific evidences. Consequently, some therapeutic options have been favored in detriment of others, and the use of others has been ruled out based on the “lack of clinical experience”.

The most outstanding and the most controversial aspects of the new consensus are detailed below as regards to the authors’ opinion, prepared by relevant representatives of both scientific societies.

Innovative aspects

Glycemic control objectives

After the recent publication of the ACCORD and ADVANCE studies, a great controversy arouse about which should the glycemic control objectives be in patients with T2D. The current consensus confirms that the objective of the glycemic control should be to reach and keep a HbA₁c <7%. No other glycemic control indexes have been included (for ex. glycemic variability) for not having been studied systematically up to date. Moreover, it ratifies the need of optimizing the treatment in case of a HbA₁c ≥7%, though it warns of the need to take into account other factors, as the life expectancy, the hypoglycemia risk and the presence of background cardiovascular disease,
considering the data arising from the last great published studies (ACCORD, ADVANCE).

**Metformin**

The metformin should be used from the beginning of the disease and as long as there is no intolerance or contraindication as regards to its use. Moreover, this consensus suggests that it can be used safely, without hypoglycemia risk in patients with “pre-diabetic hyperglycemia”, it means, before the disease starts in patients with high risk of developing T2D. Likewise, it is stated that the use of metformin is safe in patients with mild to severe renal failure and that it should not to be used in case of glomerular filtration <30 mL/min.

**Insulin titration**

The insulin is still the most efficient drug for the hyperglycemia treatment. As in the first ADA-EASD consensus, the insulin has been placed in the second therapeutic step, after the failure of the monotherapy with metformin in combination with other non-pharmacological measures. The insulin titration algorithm turns out to be especially useful and updated, which is summed up in the document figure. A reasonable initial dose of basal insulin is recommended (10 or 0.2 IU/kg), the administration in the morning for long-acting insulin analogues is also admitted (glargine, detemir), a dose increasing scheme is stated by virtue of the fasting basal glycemia and the “basal-plus” strategy is recognized implicitly, that consists of adding a dose of prandial insulin in the main intake or, at least, in which there is a higher glycemic fluctuation, as a preferable option of the insulin treatment optimization. The use of premixed insulins is not recommended during the dose adjustment phase. Later, these ones should only be used in patients in whom the prandial/basal insulin proportion is kept stable at the moment of breakfast and/or dinner.

**GLP-1 analogues**

Another novelty has been the incorporation of the GLP-1 analogues to the algorithm (exenatide), as therapeutic option in combination with other oral agents. This recognizes the GLP-1 analogues potential that, besides reducing the HbA1c in the region of 0.5-1%, reduces the weight and does not induce hypoglycemia, though the publication of isolated cases of severe pancreatitis in patients treated with these drugs is admitted.

**Criticizable points**

One of the most debatable points of the new algorithm is the division among basic and well-determined therapies (insulin, sulphonylureas), or first therapeutic option after the failure of the monotherapy with metformin, and less determined therapies, or second option. This arbitrary division seems to reply most to economists’ criteria than to the current knowledge of the disease physiopathology. The sulphonylureas, though they have a lower cost and their use has been recently revalidated (ADVANCE), induce weight gaining and a higher risk of serious hypoglycemias, and have a lower sustainability of the glycemic control (ADOPT).

**Rosiglitazone**

Since the revision of the first ADA-EASD algorithm in November 2007, published in January 2008, the contrary opinion of this group of experts to the use of rosiglitazone in T2D is known. However, the caution showed on these revision contrasts with the current frontal positioning against such drug, without having appeared since then new data that might justify this change of attitude. Notwithstanding that the authors recognize the lack of conclusive data about the potential cardiovascular risk associated to the rosiglitazone; these experts are against its use. Neither it results coherent nor reasonable that these experts point out with vehemence the use of pioglitazone (versus rosiglitazone), especially in the figure that depicts the algorithm, in spite of recognizing that the available data are “less than conclusive for … a cardiovascular disease benefit with pioglitazone”. Recent data (ACCORD, VADT) do not seem to confirm an increase of the mortality risk associated to the use of rosiglitazone. The
new studies (RECORD, BARI2D), currently ongoing, with more appropriate designs, should state the safety and efficacy of rosiglitazone definitively versus other oral agents used for the T2D treatment.

Finally, in spite of the fact that in the consensus it is stated as one of the basic principles for the selection of a particular option as regards to its capacity to allow reaching and keeping the glycemic targets, it results surprising that this advantage is not attributed explicitly to the rosiglitazone, which showed a higher sustainability of the glycemic control in monotherapy versus metformin and glibenclamide in the ADOPT study.

DPP-4 inhibitors

Like the GLP-1 analogues, the DPP-4 inhibitors or incretin potentiatros (sitagliptine, vildagliptine), represent one of the most important therapeutic novelties of the latest months. Since its commercialization, its use has been extended thanks to its efficacy, as they can be
administered by oral route (unlike the GLP-1 analogues, that are administered by subcutaneous route), even in combination with fixed doses with metformin, to the ponderal neutrality and its safety, as it does not increase the hypoglycemia risk. Especially these last characteristics confer them clear advantages versus the sulphonylureas and other secretagogue drugs, as alternatives to combine with metformin or glitazones. Therefore, the non-inclusion of these drugs to the algorithm surprise, according to these experts, given the “potential for this class of compounds to interfere with immune function”,¹ which is neither defined not stated up to date.

To sum up, the new ADA-EASD algorithm for the treatment of hypoglycemia in T2D represents an update and the consolidation of the main principles collected in its initial version. However, in spite of its virtues, the arbitrary differentiation in the selection of the several therapeutic actions, the arguable positioning versus the rosiglitazone and the lack of inclusion of the DPP-4 inhibitors, turn it in an “evolving algorithm” since its creation. Other experts, as the ones of the American College of Endocrinology and the American Association of Clinical Endocrinologists (ACE/AACE) and those of the Canadian Diabetes Association, have been able to recognize these aspects and have submitted alternative algorithms. The treatment algorithm of the Canadian Diabetes Association is depicted in figure 1,⁴ a different view and probably more clinical and less dogmatic than the new ADA-EASD algorithm.

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**References**