The chronic complications in diabetes mellitus type 2 (T2D) which influence in terms of public health are well-known by everyone. Likewise, since the publication of the results of the UKPDS and DCCT studies, we know that the reduction of the glycemic values in patients with T2D diminishes the risk of complications, primarily microvascular events. Starting from this data, different international organizations have put together clinical guide lines for the initial therapeutic management of T2D and have defined as therapeutic objective values of glycated hemoglobin (HbA1c) around a 6.5% (NICE and IDF) or a 7% (ADA and EASD).

In the global treatment diagram of patients with T2D and the control of cardiovascular risk factors, we have been able to improve certain aspects as time goes by, as the lipid or tensional profile, although in the glycemic control it has not been possible. This has been demonstrated in the rates of patients which exceed the desirable levels of HbA1c, of 63% and 69% in the United States and in Europe respectively. This fact is based, among other factors, to the progressive aspect of the pathology, in which a continuous damage of the function of the beta cell is observed, which entails the need to intensify the therapy to keep the target values of HbA1c. Such physiopathologic process has its clinic correlate in which it has been denominated as a “secondary decision”, in other words, the need to add a second drug to keep the HbA1c levels to <7% or to reach values of 8% maintaining the monotherapy treatment.

Different studies have showed that none of the strategies used at the beginning of the monotherapy treatment succeed to keep an optimum control at medium-long term. A meta-analysis showed clearly a medium fall in the HbA1c of 1% with pioglitazone, of 1.2% with rosiglitazone, of 1.1% with metformin, of 1.5% with sulfonylureas, of 0.5% with nateglinide, and of 0.8% with asacarbose. If we pay attention to the proportion of lack of effectiveness in a medium-long term, the glibenclamide was incapable of keeping the level of HbA1c below a 7%, in 53 and 71% of the patients at 3 and 6 years respectively. In this same study, metformin was not able to keep the HbA1c below the 7% in 56 and 66% of the patients at 3 and 6 years respectively. Another study, showed that between the 10 and 15% of the patients showed a secondary decision in only 36 months with metformin as first election for the monotherapy treatment. Such variation in the failure of the control showed an inverse relation in the fall of the HbA1c reached during the first year of treatment.

Before the difficulty of being able to reach the desired glycemic control and its consequences in relation to the development of a microangiopathy—as is suggested in the UKPDS study, in which significant clinical differences were found among the patients which kept medium levels HbA1c of after 6 years of 6.6 vs. 7.4%—, the recom-
mendations of the classical treatment establish the suitability to increase the dose of the drugs or continue with the scale of drug combination, although not as much in the course of action. In that way particular criterions when choosing one or another medication appear in function of the medical experience, the secondary effects, the patients tolerability, the ability of being able to follow the therapeutic indications, the economical concern and the none glycemic effects of the drugs.

Do we have arguments to defend that the early use of medication combinations could increase the effectiveness of the treatment of T2D?

The early combined use of glibenclamide/metformin or nateglinide/metformin has shown to be much more effective than the use of any of them in monotherapy. Equally useful, and with better rates of secondary effects that the use of metformin in maximum doses, the combination of a thiazolidinedione with sub-maximal doses of metformin, looking for the synergy among drugs with different action mechanisms.

The use of drugs based on incretin action show certain additional advantages to those of the glycemic control, as the positive effect on the weight and the improvement of the cardiovascular risk factors. Nowadays it is unknown if the phenomenon’s of cytoprotection of the beta cell, clearly demonstrated in animal models, can be reproducible in human beings. If this would be the case, then this type of therapy should be introduced in combination with insulin-sensitizing agents at the moment of the diagnosis, with the desire of modifying the natural course of T2D.

At a lack of clinical essays that guarantee the effectiveness of an intensive strategy of early pharmacological combination, the use of mathematic simulation methods seems to foresee benefits in the prevention of chronic complications by means of an intensive combined therapy. However, this proposal of combined therapy, complementary and intensive shall be varied when taken into practice, in light of the data recently provided by the studies ACCORD, ADVANCE, and VADT. In this sense, it seems advisable to individualize the degree and speed of intensification in the treatment of HbA1c, in terms of a decrease, probably in function of the degree of concomitant macro vascular pathology and the profile of cardiovascular drugs used, including the effect of weight gain. On the other hand, the economical aspects as well as the different drug combinations should be taken into account. Along these lines, a cost-effectiveness study recently published shows that each year the evolution of T2D implies an extra expense per patient of 75 dollars if it is adjusted by demographic factors and comorbidity, although it is highlighted that only the implantation of therapeutic intensification means an extra expense of 52 dollars per year. Our predisposition of incorporating an intensive medical treatment with early pharmacological combinations could eminently increase the cost of such treatment modality, what maybe could cause a cost-effectiveness immediate negative valuation. But in our opinion, an intensive therapy cautiously set up with an individualized valuation shall demonstrate at a long term, more years of life and of a better quality for our patients.

Using a sports comparison, we could compare T2D with a long distance running, in which to be able to aspire to the victory in the patients with T2D it is indispensable to maintain since the diagnosis an intensive and continuous treatment rhythm (but individualized in function, above all in the cardiovascular characteristics), that in this case is the minimization of the possible chronic complications. Thereby, we mediate for the use of an early pharmacological combined therapy to be able to keep a good metabolic control at long term. In this sense, we think that, just like the use of metformin has been protocolized since the diagnosis, before the impossibility of maintaining a good glycemic adjustment with lifestyle modifications, it shall be advised in an early manner the use of pharmacological combinations according to the patients’ profile.

Declaration of potential conflict of interests

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