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EDITORIAL

Targeting diarrhea-predominant irritable bowel syndrome: hopes or hypes?

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1. Introduction

Diarrhea-predominant irritable bowel syndrome (IBS-D) is one of the most frequent functional gastrointestinal disorders, recently re-classified as disorders of gut-brain interaction (DGBI), representing more than one third of all IBS patients, and features high scores of patient dissatisfaction concerning its pharmacologic treatment [1]. This is not surprising, since the pathophysiological mechanisms underlying IBS include altered brain-gut interactions, inflammation, gut dysmotility, visceral hypersensitivity, increased epithelial hyperpermeability, epigenetics and genetics, and dysbiosis [2]. These aspects then translate into lower disease-related quality of life (QoL) in IBS-D compared to patients with constipation-predominant IBS (IBS-C) [3], into the use of multiple and different treatments, and into a major psychological burden [4]. This is due to the fact that the overall benefits of the current therapeutic approaches toward IBS symptoms and pain relief are currently considered as modest [5], and we must rely on a very limited arsenal of approved drugs also featuring limited scientific evidence (see below).

2. Currently approved drugs to treat IBS-D

When including non-pharmacologic approaches, the potential therapeutic armamentarium available to treat IBS-D is huge, yet only a handful of drugs are currently approved by the Food and Drug Administration (FDA) for this indication, as evidenced by the recent guidelines provided by the American Gastroenterological Association (AGA) [6]. These drugs include eduxadoline (AGA recommendation: conditional; evidence: very low), rifaximin (AGA recommendation: conditional; evidence: very low), and alosetron (AGA recommendation: conditional; evidence: moderate), whereas there are no FDA recommendations for loperamide (AGA recommendation: conditional; evidence: very low), antispasmodics (AGA recommendation: conditional; evidence: low), and tricyclic antidepressants (AGA recommendation: conditional; evidence: low). Moreover, the AGA document was against the use of selective serotonin reuptake inhibitors in these patients. No other treatments were mentioned, and it is worth noting that alosetron is only available in the U.S.A. with important restrictions (limited to women with severe IBS symptoms), as well as eduxadoline, available in the U.S.A. and Canada (and contraindicated in patients with biliary duct obstruction, previous cholecystectomy, history of alcohol abuse, pancreatitis, and hepatic impairment). Of note, similar recommendations for IBS-D treatment have been suggested by European guidelines [7].

3. Other drugs potentially useful for IBS-D treatment

In the time course, some drugs developed for other purposes have found also indications for being possibly useful in the treatment of IBS-D, and will be examined in this section.

3.1. Mesalazine

Although potentially interesting due to its inflammatory properties, the use of this drug is not mentioned in the AGA guidelines, and it is not recommended by the European guidelines to treat IBS-D patients [7]. Moreover, a recent systematic review with meta-analysis concluded that mesalazine had, overall, only a modest efficacy on symptoms in these patients, with a low quality of evidence [8]. Thus, more high-quality randomized controlled trials are needed before recommendations for its use in IBS-D are made.

3.2. Ondansetron

This 5-HT_3 receptor antagonist is a relatively old drug used to treat nausea and vomiting following chemotherapies. Since the drug improves stool consistency, its side effects are relatively few and mild, and it has been widely available for years on the market in many countries, ondansetron has also been tested in IBS-D patients. Indeed, a recent meta-analysis showed a few beneficial effects on some symptoms (mainly stool consistency and urgency), although abdominal pain was not relieved [9]. Since the overall number of patients recruited for these studies was quite low, more robust studies involving a higher numbers of subjects are needed before recommending ondansetron as a treatment of IBS-D.

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3.3. Ramosetron

Another 5-HT_3 receptor antagonist developed for the treatment of chemotherapy-induced nausea and vomiting, this drug has been also demonstrated good efficacy in several trials conducted in IBS-D patients, and it has been commercially available in some countries for some years. However, although a recent meta-analysis including more than 1,500 subjects demonstrated the efficacy and safety of ramosetron toward all IBS-D symptoms in both sexes [10], and another network meta-analysis suggested that ramosetron has the highest efficacy in improving abdominal pain in this condition [11], this drug is presently approved only in some Eastern countries (Japan, Korea, Thailand), perhaps due to concerns of Western authorities on possible side effects similar to those reported for other drugs in this class (e.g. alosetron).

3.4. Bile acid sequestrants

Since it has been calculated that up to 30% of patients complaining of IBS-D symptoms may have an underlying malabsorption of bile acids (raising some doubt on these subjects being true IBS [12]), bile acid sequestrants (cholestyramine, colesevelam) have been tried in these patients and they are actually frequently used in clinical practice, often as second-line therapies, even though there is scarce scientific evidence for this use. Although occasional benefits may be seen, both uncontrolled and controlled studies (carried out in relatively small groups of patients) were, however, at present unable in yielding firm results on the effects of these drugs, and no recommendations may be made concerning their use.

4. New drugs under investigation for IBS-D

Due to the relative paucity of drugs approved for the treatment of IBS-D, and the relatively modest efficacy of those available, there is interest in developing new drugs for this indication, even though there is scarce likelihood that, due to either poor scientific evidence or safety concerns, effective new weapons will be soon available on the market.

4.1. β3-adrenergic receptor agonists

Two preparations belonging to this group, solabegron and vibegron, have been tested but were considered as ineffective in improving symptoms in IBS-D patients.

4.2. Ibodutant

This antagonist of tachykinin receptors NK2, after initial promising results in the approach to IBS-D patients, was not confirmed effective in subsequent trials [13], and further development was interrupted.

4.3. Olorinab

This antagonist of the cannabinoid CB 2 receptor was tested in a phase IIb randomized, controlled trial in IBS-D patients. Although the drug improved the average weekly pain scores and was well tolerated, the primary endpoint was not met; therefore, further studies are required to assess its potential usefulness.

4.4. Crofelemer

This active compound, purified from latex of *Croton lechleri*, seems able to improve some diarrheal conditions and abdominal pain in subjects with IBS. For this reason it has been tested on IBS-D female patients, but it failed in improving abdominal pain and stool consistency. However, abdominal pain was improved according to FDA monthly responder endpoint, suggesting a possible role to treat pain in these subjects [14].

4.5. Enterosgel (polymethylsiloxane polyhydrate)

Enterosgel is an intestinal adsorbent effective in acute infective diarrhea. A double-blind trial conducted in patients with IBS-D showed efficacy of enterosgel compared to placebo in reaching the primary outcome (abdominal pain and stool consistency) without significant adverse events [15], suggesting a possible use as an alternative to the limited currently available therapeutic options.

5. Conclusions

At present, treating patients with IBS-D symptoms appears to be a difficult task. This is due mainly to the fact that, apart from general basic therapeutic approaches common to all IBS subtypes, only a handful of drugs are approved for use in these patients. Besides, since the scientific evidence on the effects of these drugs is at best modest, there is quite a substantial amount of frustration among both patients and physicians. In addition, new drug development seems to suffer from a sedated pace, due to objective difficulties in recruitment (limiting the sample size) and to the various symptomatic aspects to be tackled (abdominal pain, diarrhea, stool consistency, bloating, etc.). Thus, there is the need for better and more numerous trials on candidate drugs that have demonstrated at least some efficacy, and on those with possible effectiveness demonstrated on preliminary or anecdotal studies.

6. Expert opinion

It is a matter of fact that, looking at the pharmacologic treatment of IBS-D, the present horizon appears quite meager; besides, even considering the potential of evaluating older drugs or the new drug investigative development, there seem to be more hypes than hopes.

However, this apparently pessimistic view must be interpreted under the lights of what IBS-D actually is and, given the present state of knowledge on its treatment, some considerations are needed. First, in order to obtain more consistent results we should probably better investigate these patients. In fact, IBS-D may be likely considered as a sort of 'general container,' due to the heterogeneous and complex pathophysiologic mechanisms underlying this condition. This eventually results in a spectrum of symptoms that may be extremely protean, and may overlap with that of other less frequent or misdiagnosed conditions, such as

sugars' malabsorption, microscopic colitis, bile acid malabsorption, and food intolerances [2]. Again, iatrogenic colitides (mostly featuring microscopic colonic mucosal abnormalities) may masquerade as IBS-D [16], and post-infectious IBS-D likely represents a subgroup with specific pathophysiologic features. These conditions are or cannot be always excluded *a priori*, and may somewhat 'contaminate' the clinical trials. Thus, through a better selection of patients, and especially of those recruited for pharmacologic investigations, we could likely obtain better therapeutic results by investigating more homogeneous cohorts of subjects. However, this approach is a double-edged weapon, since finding a balance between a better patients' selection by ruling out other causes as much as possible and difficulty in recruitment might be an actual problem, as shown by the recent TRITON trial [9].

Second, the concept of IBS as a 'functional' disorder should be perhaps abandoned in favor of evidences showing the presence of actual mucosal abnormalities in these patients [17], and suggesting a reclassification of this entity (possibly as an enteric neuro-gliopathy [18]). This could re-address some research interest toward new therapeutic targets, since the actual targets seem to yield relatively scarce results, at least in clinical terms. For instance, drugs developed to modulate enteric glial cells functions (involving both motor and sensitive aspects of the gut) [19] could offer new hopes for the treatment of these patients, especially concerning the pain. Third, the enormous impact on the scientific arena of the accumulating evidence on the intestinal microbiota should not let us forget that some alternatives might soon be available compared to conventional pharmacologic treatments. Indeed, although still limited by very low certainty evidence (mainly due to the extremely different species and doses of potentially beneficial bacteria investigated), there are interesting data suggesting that probiotics may be effective in relieving several or most of the symptoms complained by IBS-D patients [20]. Analogous considerations may be made for the extremely heterogeneous group of plant-derived products, whose potentialities are still largely unexplored and that have repeatedly demonstrated at least some efficacy on several symptoms in IBS-D patients [21]. However, unless specific causes for IBS-D symptoms are identified, results of studies that include a heterogeneous group of patients are likely to continue to be marginal. It is time to change the IBS-D paradigm, or we will continue to be stuck where we are.

Fortunately, the research in this field is very active, and with more and more knowledge on the basic pathophysiological mechanisms of IBS-D, the development of new drugs, and the recruitment of larger series of patients, there is hope, without hypes, of having available in the next future more effective therapeutic weapons, possibly aimed at targeting different pathophysiologic mechanisms, to treat this often disabling condition and improve the QoL of these patients.

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