

Answering Reviewers

Reviewer 1

Nassri and Ramzan present a review on pharmacologic therapy for achalasia. The manuscript is well written and very interesting. Surprisingly, a very sober-minded and unbiased comparison of different therapies is provided. My only comment is the shortness of the abstract that does not show any conclusion and does not call attention for potential readers.

Answer:

Thank you for your insightful comment. Please see the revised abstract.

Abstract

This article reviews currently available pharmacological options available for treatment of achalasia, with a special focus on the role of Botulinum toxin (BT) injection due to its superior therapeutic effect and more favorable side effect profile. The discussion on BT includes the role of different BT serotypes, better pharmacological formulations, improved BT injection techniques, the use of sprouting inhibitors, designer recombinant BT formulations and alternative substances used in endoscopic injections. The large body of ongoing research into achalasia and BT may provide a stronger role for BT injection as a form of minimally invasive, cost effective and efficacious form of therapy for patients with achalasia. The article also explores current issues and future research avenues that may prove beneficial in improving the efficacy of pharmacological treatment approaches in patients with achalasia.

Reviewer 2

Treatment of achalasia includes pharmacotherapy, endoscopic treatment and surgery. Although the long-term efficacy of pharmacotherapy is unsatisfactory, it plays an important role in the treatment of achalasia, especially when the patient is intolerable of endoscopic treatment or surgery. The author reviewed currently pharmacological options available for achalasia with a detailed review on Botulinum toxin injection (from its history, mechanism to the future direction), which helps the doctor understand the role of pharmacotherapy in the treatment of achalasia. However, several questions regarding the manuscript should be addressed. 1. In this review, the authors made a detailed review about botulinum toxin, it will be better if they could provide comparison of botulinum toxin with other treatment modalities such as endoscopic dilation, peroral endoscopic myotomy and Heller myotomy. Because this may help readers to make decision about which method would be more suitable for an individual patient.

Thank you for your detailed and insightful suggestions. Please see the changes we have made under the "Current role in treatment" heading, including detailed comparison of available modalities such as PD and myotomy.

Current role in treatment

Overall, pneumatic dilation and myotomy have superior long term efficacy than BT injection in treating patients with achalasia. [10]

In a Cochrane review comparing BT with pneumatic dilation, there was no significant difference in rates of remission at 4 weeks after intervention. However, BT was significantly less effective in maintaining symptom remission at six months and one year.[34]

Similarly, one meta-analysis analyzed studies comparing pneumatic dilation with BT injection and found a remission rate of 65.8% at one year for pneumatic dilation compared to 36% for BT injection (RR 2.20, 95% CI 1.51–3.20, $P < 0.0001$).[37]

In a prospective randomized study evaluating BT injection with Heller myotomy, the authors found that results at 6 months were comparable; however, the efficacy of BT injection decreased thereafter and the probability of being symptom free at 2 years was 87.5% after Heller myotomy and only 34% after BT injection ($p < 0.05$).[36]

Peroral endoscopic myotomy in a novel endoscopic treatment for achalasia which is a minimally invasive alternative to conventional Heller myotomy. Although to our knowledge no prospective trials have compared BT injection to POEM, various studies have compared Heller myotomy with POEM and found favorable results. One meta-analysis evaluating a total of four studies found that POEM had comparable complications (odds ratio [OR] =1.17, 95% confidence interval [CI] 0.53-2.56, $P = 0.70$) and symptom recurrence (OR=0.24, 95% CI 0.04-1.55, $P = 0.13$) as with Heller's Myotomy on short term follow up.[38]

2. It would be better if the authors could provide the indication of pharmacotherapy or botulinum toxin, as "For these reasons, BT injection is not considered a first line therapy except in certain high risk patient populations, such as elderly patients and patients with extensive co-morbidities, or for salvage therapy" is not a clear criteria.

Again thank you for pointing this out.

Please see the changes we have made under the "Current Role in Treatment" Heading, which goes through the indications in details and the rationale and data behind them, as well as the references to several expert review articles.

"The response to BT seems to be unaffected by prior therapy such as prior pneumatic dilation or myotomy, which highlights an important role for BT injection in patients who have failed prior surgical or endoscopic therapy. In one study, [39] the response to BT injection in achalasia were compared in patients without prior therapy, with prior dilation and with prior myotomy. Neither LES pressures nor symptoms scores differed between groups. At 6 months the remission rate was 71.4 % in those who received prior dilation, 71.4 % in prior myotomy and 73.9% in prior BT injection.

Pneumatic dilation comes with recognized risks, including esophageal perforation (~1.6%) as well as symptomatic heartburn in up to 45% of patients at four years of follow up. [34] Likewise, myotomy may be associated with risks, most noticeably esophageal perforation and postoperative GERD [40], and due to the nature of the procedure may not be suitable for patients with multiple comorbidities or at high risk.

For this reason, several expert guidelines have suggested that BT injection may play a role in elderly patients and patients with extensive co-morbidities, as well as for salvage therapy. [1, 40-44]"

3. I could not agree with you on the sentence "Despite this, a recent analysis [41] of practice patterns in the United States has shown that BT injection was the most frequently used initial endoscopic therapy" in Current role in treatment and "BT injection into the LES is the most commonly used initial therapy in patients with achalasia." in the conclusion part for the next four reasons: ① As far as we know and as you said "BT injection is not considered a first line therapy except in certain high risk patient populations", we do not think BT injection is the most commonly used initial therapy in achalasia; ② The treatment of achalasia changed to some extent during the past four year, and the reference 41 was published in 2011 and the data analyzed was during 2000-2008, so it may not well reflect the current situation; ③ In my opinion, the most commonly used initial therapy in patients with achalasia should be dilation with 51% (balloon dilation in 21%, Savary dilation in 20%, Maloney dilation in 10%) in reference 41; ④ The reference 41 was not an international database, and it was only about the information in

USA.

We have removed this reference and changed the “Current Role in Treatment” as above.

4. There are a few English grammatical and/or spelling mistakes.

Thank you. These have now been addressed.