Systematic Review of Currently Available Therapies for Crohn's Disease and Ulcerative Colitis

HELLENIC REPUBLIC
National and Kapodistrian University of Athens

M. Zoga[1], C. Kani[2], K. Souliotis[3], S.L. Markantonis[1]

[1]Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Athens, Greece, [2] University Research Institute of Maternal and Child Health &Precision Medicine, and UNESCO Chair on Adolescent Health Care, Athens, Greece, [3] University of Peloponnese, Department of Social and Educational Policy, Corinth, Greece

INTRODUCTION

Inflammatory bowel disease (IBD) is a term that encompasses both Ulcerative colitis (UC) and Crohn's disease (CD), disorders involving chronic inflammation of the digestive tract. UC involves inflammation located in the superficial lining of the colon and the rectum, while CD involves inflammation that can be located in deeper layers of the digestive tract. The steady increase in IBD patient numbers emphasizes the need to intensify the search for more effective and safer treatments, such as biological treatments.

OBJECTIVES

To conduct a systematic review and meta-analysis regarding the efficacy and safety of some biological therapies, specifically adalimumab (ADA), golimumab (GLM), infliximab (IFX), ustekinumab (UST) and vedolizumab (VDZ), and the janus kinase (JAK) inhibitor, tofacitinib (TOFA). inhibitor, tofacitinib (TOFA).

METHODS

INCLUSION CRITERIA

- Randomized Controlled Trials (RCTs) studying the efficacy and safety of at least one of the following biologics vs. placebo (PLB): ADA, GLM, IFX, UST, VDZ, TOFA
- Adult participants of both genders
- Diagnosis of Crohn's disease or Ulcerative Colitis in active phase with chronic and acute inflammation

LITERATURE SEARCH

- PubMed/Medline
- The Cochrane Library
- European Medicines Agency
- International Clinical Trials Registry Platform
- Science Direct

OUTCOMES

- Clinical remission
- Clinical Response
- Adverse events (AEs)
- Discontinuation due to AEs
- Infection
- Serious Infection

RISK OF BIAS

The selected studies were assessed using robvis software, according to the Cochrane Risk of Bias tool.

META-ANALYSIS

- At least two randomized double-blind studies were required for each of the biological therapies included.
- The software Review Manager was used, with a fixed effect statistical model. The estimated risk difference (RD) values were used as a measure of the likely benefits and likely harms of the interventions and the 95% confidence intervals were reported. Data quality was assessed according to the GRADE system.

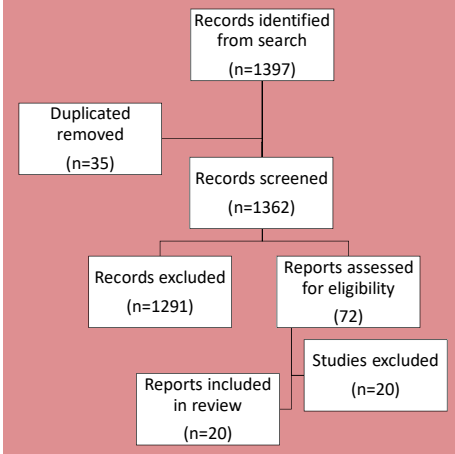

Figure 1: Flow diagram

RESULTS

The literature search resulted in 1397 studies, 17 of which met the inclusion criteria (**Figure 1**). The meta-analysis resulted in 7 comparisons (2 for ADA, IFX and UST, 1 for TOFA), but GLM and VDZ data could not be compared, due to lack of study design similarity (different dosage, different frequency of administration).

→The estimated RD (Risk Difference) values favoured ADA over PLB (p<0.00001) for Clinical Remission and Clinical Response with 40 mg/every week doses (**Figure 2** for Clinical Remission estimated RD 0.19 CI 95% [0.13, 0.25]), **Figure 3** for Clinical Response estimated RD 0.18 CI 95% [0.12, 0.25]) and 40 mg/every other week doses (for Clinical Remission estimated RD of 0.17 CI 95% [0.11, 0.23] and for Clinical Response RD of 0.16 CI 95% [0.10, 0.23]) (p<0.00001), as well as for cases of discontinuation due to AE (p=0.0004 and p=0.01, respectively).

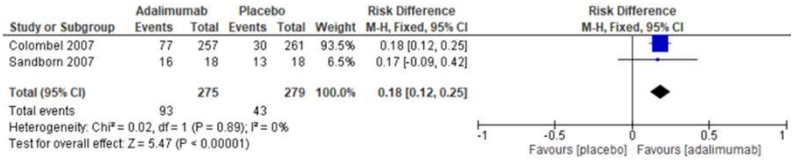

Figure 2: *Forest plot diagram* for Clinical Remission of ADA 40 mg/every week vs PLB

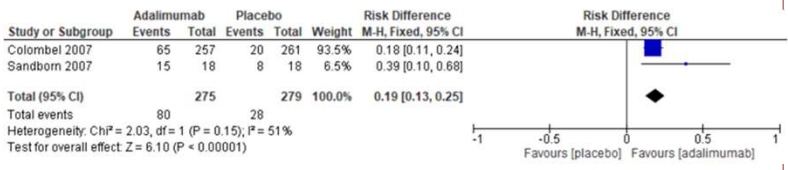

Figure 3: *Forest plot diagram* for Clinical Response of ADA 40 mg/every week vs PLB

→RD data favoured Clinical Remission and Clinical Response with IFX vs. PLB for 5 mg and 10 mg doses (p<0.00001 for 8 and 30 weeks of therapy), except for Clinical Response with 10mg for 8 weeks (p=0.008). For Clinical Remission estimated RD values were 0.26 CI 95% [0.19, 0.33] and 0.19 CI 95% [0.13, 0.26] for the 8th week, and 0.17 CI 95% [0.10, 0.24] and 0.23 CI 95% [0.16, 0.31] for the 30th week.

For Clinical Response with IFX 5 mg doses estimated RD values were 0.34 CI 95% [0.25, 0.42] and 0.22 CI 95% [0.13, 0.30] for 8 and 30 weeks of therapy, respectively, while for IFX 10 mg doses estimated RD values were RD of 0.12 CI 95% [0.03, 0.20] and 0.32 CI 95% [0.24, 0.40] for 8 and 30 weeks of therapy, respectively.

→Regarding UST 130 mg, RD data for Clinical Remission favoured the drug over PLB after 3, 6 and 8 weeks of therapy (p=0.02, p=0.0002 and p<0.0001, respectively) as well as for Clinical Response (p=0.001, p<0.00001 and p<0.00001, respectively). RD data for Clinical Remission and Clinical Response favoured UST 6 mg/kg over PLB (p<0.0001 for 3, 6 and 8 weeks of therapy).

→Estimated RD data for Clinical Remission and Response favoured TOFA over PLB with an estimated RD of 0.14 CI 95% [0.10, 0.18] and 0.26 CI 95% [0.20, 0.32] (p<0.00001 and p<0.00001, respectively).

CONCLUSIONS

Based on clinical remission and clinical response data, the results of the meta-analysis suggest that the biologics ADA, IFX, UST, and the JAK inhibitor, TOFA, are more effective than PLB for IBD therapy, but safety data are inconclusive.

References:

Colombel JF. et al. (2007) Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology; 132(1):52-65

Feagan BG. et al. (2013) GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med; 369(8):699-710

Feagan BG. et al. (2016) UNITI–IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's Disease. N Engl J Med; 375(20):1946-1960

Rutgeerts P. et al. (**2015**) PURSUIT-IV study group. Randomized clinical trial: a placebo-controlled study of intravenous golimumab induction therapy for ulcerative colitis. Aliment Pharmacol Ther; 42(5):504-14

Sandborn WJ. et al. (2014) PURSUIT-Maintenance Study Group. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology; 146(1):96-109

Sandborn WJ. et al. (2014) PURSUIT-SC Study Group. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology; 146(1):85-95

Sandborn WJ. et al. (2013) GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med; 369(8):711-21

Sandborn WJ. et al. (2007) Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut; 56(9):1232-9

Sandborn WJ. et al. (2012) Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med; 367(7):616-24

Rutgeerts P. et al. (2005) Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med; 353(23):2462-76