Pharmacological Reports 68 (2016) 1237–1243

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original article

Safety profile of biologic drugs in the therapy of Crohn disease: A systematic review and network meta-analysis

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ARTICLE INFO

Article history:
Received 30 June 2016
Received in revised form 29 July 2016
Accepted 30 July 2016
Available online 1 August 2016

Keywords:
Biologic drugs
Network meta-analysis
Safety profile
Systematic review
Crohn disease

ABSTRACT

Background: Crohn disease (CD) is an inflammatory bowel disease which occurs especially in developed countries of Western Europe and North America. The aim of the study was to compare the safety profile of biologic drugs in patients with CD.
Methodology: A systematic literature search was performed using PubMed, Embase, and CENTRAL databases, until April 27, 2016. We included randomized controlled trials (RCTs) that compared the safety of biologic drugs (infliximab, adalimumab, vedolizumab, certolizumab pegol, and ustekinumab) with one another or with placebo in patients with CD. The network meta-analysis (NMA) was conducted for an induction phase (6–10 weeks) and maintenance phase (52–56 weeks) with a Bayesian hierarchical random effects model in the ADDIS® software. The PROSPERO registration number was CRD42016032606.
Results: Ten RCTs were included in the systematic review with NMA. In the case of the induction phase, the NMA could be conducted for the assessment of the relative safety profile of adalimumab, vedolizumab, certolizumab pegol, and ustekinumab, and in the case of the maintenance phase—of infliximab, adalimumab, and vedolizumab. There were no significant differences in the rate of adverse events in patients treated with biologics. Statistical analysis revealed that vedolizumab had the greatest probability of being the safest treatment in most endpoints in the induction phase and adalimumab—in the maintenance phase.
Conclusions: No significant differences between the biologics in the relative safety profile analysis were observed. Further studies are needed to confirm our findings, including head-to-head comparisons between the analyzed biologics.
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Introduction

Crohn disease (CD) is an inflammatory bowel disease of unknown etiology [1–3]. It is a transmural, granulomatous inflammation that can affect any part of the gastrointestinal tract [2]. Worldwide, the estimated incidence of CD ranges from 5 to 15 cases per 100,000 person-years, while the prevalence amounts to about 50–200 cases per 100,000 inhabitants [2–4].

Different pharmacological methods can be used in the treatment of CD. Several biologic drugs, such as tumor necrosis factor (TNF) inhibitors (infliximab and adalimumab) or integrin antagonist (vedolizumab) have been approved for the treatment of CD by the European Medicines Agency (EMA) in the European Union as well as by the Food and Drug Administration (FDA) in the United States; certolizumab pegol was registered for the treatment of CD by the FDA. Ustekinumab has not been approved either by the EMA or FDA for the treatment of patients with CD, but currently undergoes authorization procedures by both organizations [5].

If direct head-to-head evidence on the safety profile is lacking, indirect evidence may facilitate decision making based on the evaluation of toxicity of biologics. Therefore, we applied a network met-analysis (NMA), which is a validated method for multiple adjusted indirect comparisons and is one of the most suitable approaches to indirect treatment comparisons of randomized controlled trials (RCTs). It allows a simultaneous comparison of numerous therapeutic options (at least 3), taking into account the results of direct and indirect comparisons at the same time [6–9].

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http://dx.doi.org/10.1016/j.pharep.2016.07.013
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The aim of this systematic review with NMA was to compare the safety profile of biologic drugs in patients with CD.

Methodology

Data sources and searches

The systematic review was conducted and reported according to the PRISMA Extension Statement for Reporting of Systematic Reviews incorporating NMA [8], recommendations for conducting and interpreting NMAs (developed by the ISPOR Task Force [9] and Cipriani et al. [7]), and the Cochrane Handbook [10]. The study protocol was prespecified and registered online on PROSPERO (CRD42016032606) [11]. Medline via PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to April 27, 2016. We used medical subject heading (MeSH and Emtree) terms combined with Boolean logical operators (Supplementary material, Table 1). The reference lists of the included studies were screened to identify additional eligible studies. RCTs comparing and evaluating the safety profile of biologic drugs (infliximab, adalimumab, vedolizumab, certolizumab pegol, and ustekinumab) with one another (head-to-head trials) or with placebo in patients with CD were included. All searches were limited to RCTs in humans, published in English.

Study selection

Two reviewers independently conducted the search, using the same search strategy and selection of studies on the basis of the previously established inclusion criteria. The same 2 reviewers independently screened all titles, abstracts, and full-length texts identified in the searches. Any discrepancies were resolved by consensus with the third reviewer. There was a high degree of agreement between the reviewers (89%). Studies were selected for inclusion based on the following criteria: 1) RCT (placebo-controlled or head-to-head trials); and 2) patients older than 15 years of age with active CD as defined by conventional clinical, radiographic, and endoscopic criteria (CD activity index >150). Nonrandomized or uncontrolled open-label studies as well as unpublished studies and conference abstracts were not included, due to the lack of appropriate data and detailed information about the methodology and study results. Full-text articles were included if they contained information on the study population, treatment regimen, and necessary data to extract. We selected only those biologics that have been registered by the EMA or by the FDA for the treatment of CD. Additionally, we included ustekinumab, a novel biologic drug currently undergoing the approval process by the EMA and FDA for the therapy of patients with CD. We included studies relating to the induction phase (follow-up of 6–10 weeks) and the maintenance phase (follow-up of 52–56 weeks), enabling the assessment of the safety profile. In the safety analysis, we took into consideration all available endpoints that occurred a priori with a frequency of at least 3%.

Data extraction and quality assessment

Studies that met the inclusion criteria were independently reviewed by 2 reviewers who extracted the following information: participants' characteristics, study design, intervention and regimen details, duration of treatment, follow-up, and proportion of participants achieving particular predefined outcomes (safety profile). Those data allowed us to assess the clinical heterogeneity on the basis of characteristics of the included studies. The results from the included studies were analyzed separately for the induction phase and maintenance phase. Because the studies included different dose regimens, we extracted and analyzed only data from trial groups that adhered to the dose regimens approved by the EMA or FDA. Studies with unapproved dose regimens were excluded from the analysis. In the case of multi-arm trials using biologic drugs, relevant data were extracted only for the arms with an approved regimen and for the placebo arm. Different doses of the same biologic drugs were pooled together. The same 2 researchers evaluated the quality of the included studies, using a tool for assessing risk of bias recommended by the Cochrane Collaboration, namely, domain-based evaluation ("+", low risk of bias; "−", high risk of bias; "?", unclear risk of bias) [10]. All ambiguities were resolved by consensus with the third reviewer.

Statistical analysis

To calculate direct estimates of treatment effect for placebo, we conducted a pair-wise meta-analysis within a DerSimonian-Laird random effects meta-analysis in the Review Manager software, version 5.3. The pair-wise meta-analysis between interventions with placebo was conducted to confirm the results obtained in the framework of the NMA. If the pair-wise meta-analysis for a particular endpoint could not be performed, we calculated odds ratios (ORs) with 95% confidence intervals (CIs). In the absence of a possibility to conduct a meta-analysis, we calculated ORs with 95% CIs. Statistical evaluation of heterogeneity was assessed by using the I^2 parameter. The value of I^2 ranges from 0% to 100%, where 0%

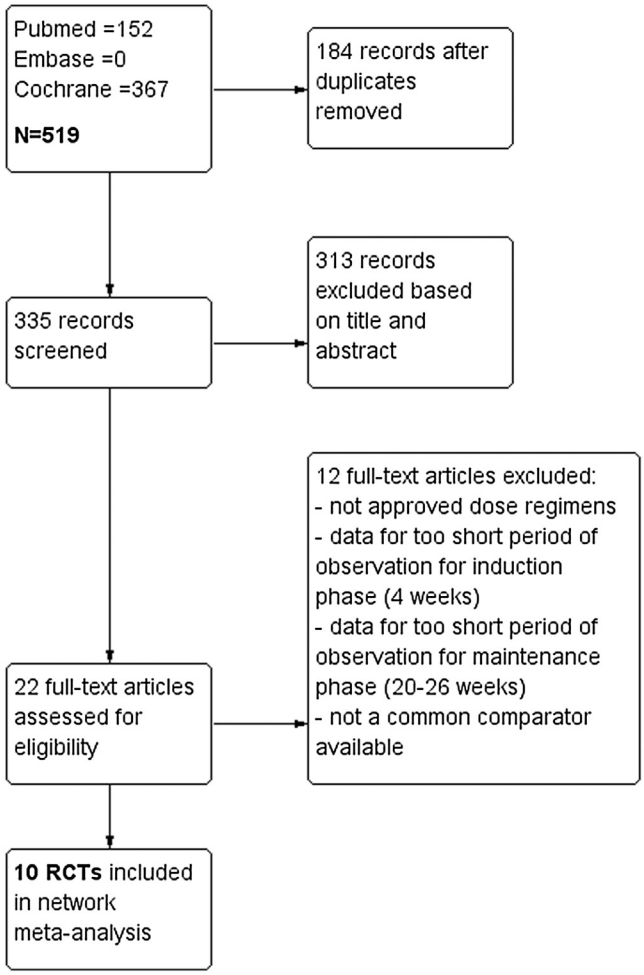

Fig. 1. Study flow diagram showing the results of the systematic review and the process of screening and selecting studies for inclusion in the network meta-analysis.

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