Monoclonal Antibodies as Analgesia of Chronic Low Back Pain: a Systematic Review and Meta-analysis of Efficacy and Safety

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Abstract

Introduction. *Monoclonal antibodies (mAb) emerged as a possible option in addressing the partial response to current treatment modalities in chronic low back pain (CLBP).*

Objective: *to evaluate the efficacy and safety of mAb for CLBP.*

Materials and Methods*. Randomized controlled trials on adult patients with CLBP who received mAb-therapy compared to those who did not as a control group. The result was the changes in Low Back Pain Intensity (LBPI) Numeric Rating Score and Roland–Morris Disability Questionnaire (RMDQ) indicating improved pain, disability, and the risk of adverse events. Meta-analysis, risk of bias, and confidence in the evidence for each analysis were assessed. We* ***aimed*** *at reviewing current treatment methods for degenerative lumbosacral spinal stenosis with an emphasis on surgical treatment methods.*

Results*. Six studies were included, with a total of 3851 participants. mAb significantly reduce LBPI and RMDQ score (weighted mean difference –1.48; 95% CI –2.63 to –0.33; p = 0.01). Tanezumab and fasinumab were significantly reduced both LBPI (weighted mean difference of –4.11; 95% CI –6.27 to –1.95; p = 0.0002 and weighted mean difference –0.24; 95% CI –0.47 to –0.02; p = 0.04 respectively) and RMDQ scores (weighted mean difference –3.72; 95% –5.48 to –1.97 and weighted mean difference –0.50; 95% –0.73 to –0.26 respectively, both p < 0.0001). The mAb have significantly greater odds of any adverse events (OR 1.23; 95% 1.06 to 1.43; p = 0.007) but no greater odds regarding serious adverse events (OR 1.00; 95% 0.69 to 1.46; p = 0.98).*

Conclusion*. Depending on the types of drugs used, mAb had a favorable outcome and were relatively safe in reducing LBPI and RMDQ scores.*

Keywords: *monoclonal antibody; tanezumab; fasinumab; fulranumab; denosumab; chronic low back pain; LBPI; RMDQ*

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Применение моноклональных антител в качестве анальгетиков при хроническом болевом синдроме в нижней части спины: систематический обзор и метаанализ эффективности и безопасности

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Аннотация

Введение. *Моноклональные антитела (мАТ) всё чаще рассматриваются как возможное средство для достижения частичного ответа при хроническом болевом синдроме (ХБС) в нижней части спины.*

Цель: *изучить эффективность и безопасность мАТ при ХБС в нижней части спины.*

Материалы и методы*. Проведены рандомизированные контролируемые исследования с участием взрослых пациентов, страдающих ХБС в нижней части спины и получавших мАТ, и контрольной группы, не получавшей мАТ. Выявляли изменение оценки по числовой оценочной шкале выраженности боли в нижней части спины (LBPI) и опроснику Роланда–Морриса для определения уровня инвалидизации (RMDQ), отражающие уменьшение боли, сопутствующей инвалидизации, а также риск нежелательных явлений. Нами подготовлен метаанализ и проанализированы риск систематических ошибок и доказательная сила каждого отдельного анализа.*

Результаты*. В обзор вошли 6 исследований, в которых участвовал в общей сложности 3851 пациент. Применение мАТ привело к значимому снижению оценки по LBPI и RMDQ: средневзвешенная разница –1,48; 95% доверительный интервал (ДИ) (–2,63; –0,33), p = 0,01. На фоне применения танезумаба и фасинумаба отмечалось значимое снижение балла по LBPI (танезумаб – средневзвешенная разница –4,11; 95% ДИ (–6,27)–(–1,95), p = 0,0002; фасинумаб – средневзвешенная разница –0,24; 95% ДИ (–0,47)–(–0,02); p = 0,04) и RMDQ (танезумаб – средневзвешенная разница –3,72; 95% ДИ (–5,48)–(–1,97); p < 0,0001; фасинумаб – средневзвешенная разница –0,50; 95% ДИ (–0,73)–(–0,26); p < 0,0001). На фоне применения мАТ значимо увеличивался риск развития любых нежелательных явлений (отношение шансов 1,23; 95% ДИ 1,06–1,43; p = 0,007), однако риск развития серьёзных нежелательных явлений не повышался (отношение шансов 1,00; 95% ДИ 0,69–1,46; p = 0,98).*

Заключение*. В зависимости от препарата применение мАТ приводило к благоприятному исходу с уменьшением оценки по LBPI и RMDQ и было относительно безопасным.*

Ключевые слова*: моноклональное антитело; танезумаб; фасинумаб; фулранумаб; деносумаб; хроническая боль в нижней части спины; LBPI; RMDQ*

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage[1]. Pain is responsible for informing the body of the danger, while chronic pain becomes a disease, losing its function of signaling a danger and producing suffering for the patient. Low back pain is a common reason for presentation to emergency departments, general practice and rehabilitation services worldwide [1]. Even after treatment, many patients report persistent pain and severe disability ⩾ 3 months after the first episode. Many patients with chronic pain, especially chronic low back pain (CLBP), remain challenging to treat and respond only partially to currently available treatment options [2]. Monoclonal antibodies (mAb) may address an unmet need for patients with CLBP that is unresponsive or poorly tolerant to conventional forms of treatment. In this setting, mAb have emerged as a possible option [3].

mAb are artificially produced antibodies for therapeutic purposes developed from single animal or human cell lines. They consist of large B-cell-derived glycoproteins made up of two heavy and two light chains held together by disulfide bonds to form a Y-shaped protein. They are typically derived from the Y-immunoglobulin (or IgG) isotype [4]. The hypervariable regions of each heavy and light chain combine to form the antigen binding site, referred to as the fragment antigen binding domain. In contrast, the crystallisable or constant fragment domain responsible for the effector function comprises two regular domains [4, 5]. Advances in preclinical and clinical research have led to the development of biological agents targeting specific cytokines in the potentiation and transmission of pain in CLBP where inflammatory processes occur; these targets are mainly nerve growth factor (NGF) and tumour necrosis factor (TNF) [5, 6]. The efficacy and safety of mAb for CLBP still faces challenges because of the lack of research. This systematic review and meta-analysis aims to evaluate the efficacy and safety of mAb in patients with CLBP.

Materials and methods

Protocol and registration

This systematic review and meta-analysis reported the literature findings according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2021 [7]. The protocol of this review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database with the registration number CRD42023449999.

Search Strategy

A literature search was conducted across published studies from January 2011 to July 2023 and was not limited to any language. We searched the literature on 16 July 2023 across the Pubmed, NCBI, Google Scholar, Science Direct, Europe PMC and Cochrane Central Register of Controlled Trials (CENTRAL) databases. The keywords used in each database are presented in the Table 1.

Inclusion and exclusion criteria

This systematic review included randomised controlled trial reports in adult patients (over 18 years) with CLBP who received mAb-therapy compared to those who did not receive mAb as a control group. In this case, the control group can be placebo or other treatments other than mAb plus placebo. This study includes patients with CLBP defined as more than 12 weeks or more than 3 months, not limited to any severity grade. The primary results are changes in the Low Back Pain Intensity (LBPI) Numeric Rating Score, indicating pain improvement and changes in the Roland–Morris Disability Questionnaire (RMDQ) indicating improvement in pain-related disability. The secondary outcome is the risk of adverse events in patients receiving mAb and controls. The exclusion criteria are research on animals, non-randomised controlled trials, studies without full-text reports, studies with using only active substance as control (non-placebo control) and studies in participants with a history or evidence of spinal disease (e.g. malignancy, fracture, trauma, spondyloarthritis, infection, former low back surgery, autoimmune disease, and mental disorders). Literature reviews were screened for references that could be used before they were excluded.

Data extraction

Data were collected in a standard format, including study citations, demographic characteristics of the participants (age, sex), number of patients, daily dose intervention, regimen, mAb classification, mAb target, comparison, outcome, and safety data (adverse events). The adverse events in this study were analysed based on the number of participants who reported any adverse event during treatment.

Assessment of quality and risk of bias in the included studies

The authors performed a preliminary search and quality assessment of each included analysis using the Jadad

[1] International Association for the Study of Pain. IASP Taxonomy. URL: http://www.iasp-pain.org/Taxonomy

Table 1. Keywords (MeSH) that have been used in every database

Database	Medical subject heading	Number of studies found
PubMed	(«monoclonal antibody»[All Fields] AND «chronic low back pain»[All Fields]) AND ("treatment"[All Fields])	47
NCBI	((((«antibodies, monoclonal»[Supplementary Concept] OR «antibodies, monoclonal»[All Fields] OR «monoclonal antibodies»[All Fields] OR «antibodies, monoclonal»[MeSH Terms] OR («antibodies»[All Fields] AND «monoclonal»[All Fields]) OR («monoclonal»[All Fields] AND «antibodies»[All Fields])) AND (chronic[All Fields] AND («low back pain»[MeSH Terms] OR («low»[All Fields] AND «back»[All Fields] AND «pain»[All Fields]) OR «low back pain»[All Fields]))) AND («therapy»[Subheading] OR «therapy»[All Fields] OR «treatment»[All Fields] OR «therapeutics»[MeSH Terms] OR «therapeutics»[All Fields])) AND («randomized controlled trial»[All Fields] OR «randomized controlled trials as topic»[MeSH Terms] OR «randomized controlled trial»[All Fields] OR «randomised controlled trial»[All Fields]) AND («2010/01/01»[PubDate] : «2023/12/31»[PubDate])	2017
Google Scholar	"monoclonal antibody" AND "chronic low back pain" AND "treatment" AND "randomized controlled trial"	399
Science Direct	«monoclonal antibody» AND «chronic low back pain» AND «treatment» AND «randomized controlled trial»	48
Europe PMC	«monoclonal antibody» AND «chronic low back pain» AND «treatment» AND Randomized Controlled Trial AND (((SRC:MED OR SRC:PMC OR SRC:AGR OR SRC:CBA) NOT (PUB_TYPE:»Review»)))	86
Cochrane Central Register of Controlled Trials (CENTRAL)	"monoclonal antibody" AND "chronic low back pain" AND "treatment" AND "randomized controlled trial"	18

Scale Assessment for randomised controlled trials, where a score of 3 to 4 is deemed moderate high-quality studies. In contrast, a score of higher than 4 indicated high-quality studies [8].

Review team members assessed the risk of bias using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions [9] The evaluation items included the following seven domains:

- random sequence generation;
- allocation concealment;
- blinding (participants and personnel);
- blinding (outcome assessment);
- incomplete outcome data;
- selective outcome reporting;
- 'other bias' (comparability of treatment and control group at entry, and post-randomisation recruitment bias in studies with cluster allocation).

According to the extracted information, each item of the included studies was classified into three levels: "low risk of bias", "unclear risk of bias", or "high risk of bias". Where necessary, we contacted the study authors for clarification. Disagreements were resolved by discussion between the review authors and where necessary. The confidence in the evidence for each analysis using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [9].

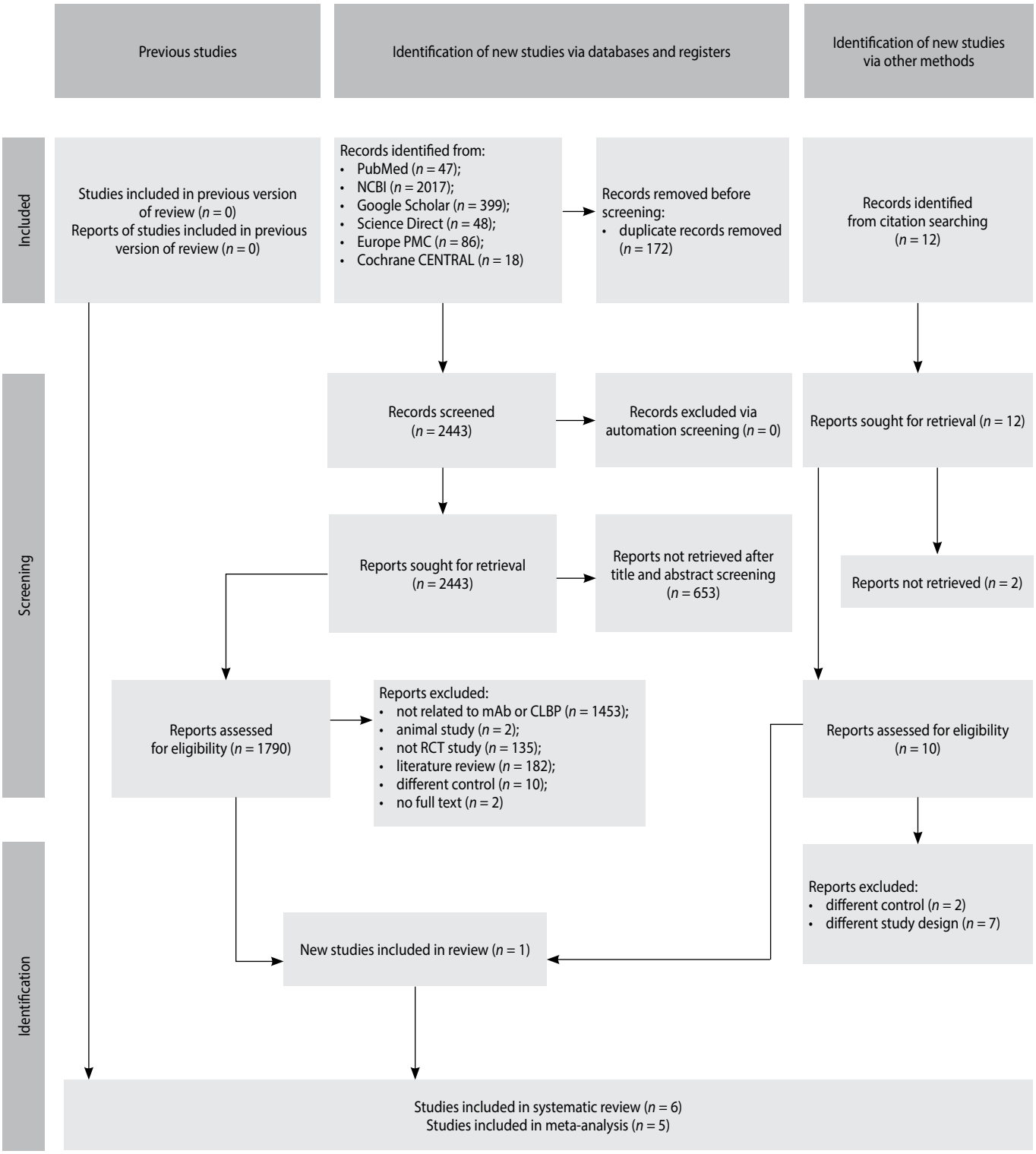

Fig. 1. PRISMA flow diagram for the included study.

Table 2. Risk of bias in included studies based on Cochrane Risk of Bias Tool

Study	Random sequence generation)	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete data (high < 80%)	Selective reporting	Other bias
Markman J.D. et al. (2020)	Low	Low	Low	Low	High	Low	Low
Katz N. et al. (2011)	Unclear	Unclear	Low	Low	Low	Low	Unclear
Kivitz A.J. et al. (2013)	Unclear	Unclear	Low	Low	Low	Low	Unclear
Dakin P. et al. (2021)	Low	Low	Low	Unclear	Low	Low	Unclear
Sanga P. et al. (2016)	High	Unclear	Low	Low	High	Low	Unclear
Cai G. et al. (2018)	Low	Low	Low	Low	Low	Low	Low

Table 3. LBPI and RMDQ score changes from baseline to endpoint ($M \pm m$)

Author (year)	Changes in LBPI score from baseline		Changes in RDMQ score from baseline		Duration of treatment
	monoclonal antibody group	control group	monoclonal antibody group	control group	
Markman J.D. et al. (2020)	NA	NA	NA	NA	16
Katz N. et al. (2011)	–3,17 ± 0,24	–2,41 ± 0,34	NA	NA	6
Kivitz A.J. et al. (2013)	–1,97 ± 0,29	–1,25 ± 0,16	–2,82 ± 0,42	–1,75 ± 0,29	16
Dakin P. et al. (2021)	–2,41 ± 2,04	–1,9 ± 2,1	–6,28 ± 5,30	–3,8 ± 4,5	16
Sanga P. et al. (2016)	–2,05 ± 1,98)	–2,0 ± 2,17)	NA	NA	12
Cai G. et al. (2018)	–6,0 ± 2,0	–3,0 ± 1,9	–1,6 ± 1,4	–1,8 ± 1,3	26

Note. NA — not accessed.

Statistical analysis

Review Manager 5.4 software was used to perform this meta-analysis. The primary outcome of this study is the difference in LBPI and RMDQ scores. We calculated the weighted mean difference and 95% confidence intervals (CI) for changes from the baseline level in the mAb-group *vs* the control group. We calculated the odds ratio (OR) and 95% confidence intervals (CI) for the risk of adverse events in both groups. A random-effects model was used when $I^2 > 50\%$ or $p < 0.1$; when $I^2 \leqslant 50\%$ and $p > 0.1$, a fixed-effect model was used to merge the data. The degree of heterogenicity was assessed based on the I^2 statistics A value of $I^2 < 25\%$ was deemed low heterogenicity, 26–50% moderate heterogenicity, and > 50% high heterogenicity. Subgroup analyses were done based on each drug used (denosumab, fasinumab, tanezumab, fulnarumab).

Agent; study	Dose, route of administration	Monoclonal antibody			Placebo			Weight, %	Std. mean difference; IV, fixed; 95% CI
		M	*m*	total	*M*	*m*	total		
Denosumab; Cai G. et al. (2018)	60 mg SC	–6	5.4525	31	–3	5.6986	37	2.5	–0.53; (–1.02)–(–0.04)
	Subtotal			31			37	2,5	–0.53; (–1.02)–0.04
	Heterogeneity: not applicable								
	Test for overall effect: Z = 2.14; *p* = 0.03								
Tanezumab; Katz N. et al. (2011)	20 µg/kg IV once	–3.17	2.2514	88	–241	2.1771	41	4.3	–0.34; (–0.71–0.03
Tanezumab; Kivitz A.J. et al. (2013)	10 mg/kg IV every 8 weeks	–2.06	2.4046	295	–125	2.4265	230	19.8	–0.34; 0.51–(–0.16)
	20 mg/kg IV every 8 weeks	–2.18	2.4046	295	–125	2.4265	230	19.8	–0.38; –(–0.56)–(–0.21)
	5 mg/kg IV every 8 weeks	–1.58	2.437	232	–1.25	2.4265	230	17.9	–0.14; (–0.32)–0.05
	Subtotal			910			731	61.8	–0.29; (–0.39)–(–0.19)
	Heterogeneity: $\chi^2 = 4.21$; df = 3 (*p* = 0.24); $I^2 = 29\%$								
	Test for overall effect: Z = 2.14 (*p* < 0.00001)								
Fulranumab; Sanga P. et al. (2016)	10 mg SC every 4 weeks	–2.1	2.18	77	–2	2.17	76	6.0	–0.05; (–0.36)–0.27
	1 mg SC every 4 weeks	–1.9	2.14	77	–2	2.17	76	6.0	–0.05; (–0.27)–0.36
	3 mg SC every 4 weeks	–2.2	1.89	77	–2	2.17	76	5.9	–0.10; (–0.41)–022
	6 mg LD + 3 mg SC every 4 weeks	–2	1.72	78	–2	2.17	76	6.0	0.00; (–0.32)–0.32
	Subtotal			309			304	23.8	–0.02; (–0.18)–0.13
	Heterogeneity: $\chi^2 = 0.44$; df = 3; *p* = 0.93; $I^2 = 0\%$								
	Test for overall effect: Z = 0.30; *p* = 0.76								
Fasinumab; Dakin P. et al. (2021)	6 mg SC every 4 weeks	–2.1	1.9	48	–1.9	2.1	49	3.8	–0.10; 0.50–0.30
	9 mg SC every 4 weeks	–2.6	2	55	–1.9	2.1	49	4.0	–0.34; (–0.73)–0.05
	9 mg SC every 8 weeks	–2.5	2.2	56	–1.9	2.1	49	4.0	–0.28; (–0.66)–0.11
	Subtotal			159			147	11.8	–0.24; (–0.47)–(–0.02)
	Heterogeneity: $\chi^2 = 0.77$, df = 2; *p* = 0.68; $I^2 = 0\%$								
	Test for overall effect: Z = 2.09; *p* = 0.04								
Total				**1409**			**1219**	**100.0**	**–0.23; (–0.31)–(–0.15)**
Heterogeneity: $\chi^2 = 14.96$; df = 11; *p* = 0.18; $I^2 = 26\%$									
Test for overall effect: Z = 5.80; *p* < 0.00001									
Test for subgroup differences: $\chi^2 = 9.55$; df = 3; *p* = 0.02; $I^2 = 68.6\%$									

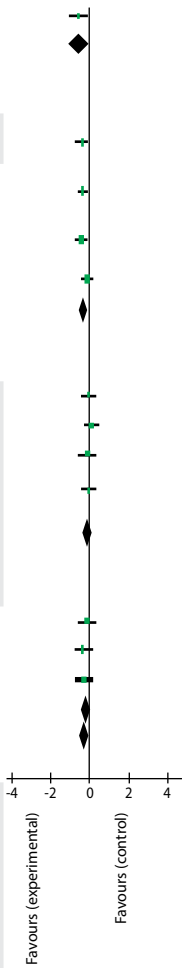

Fig. 2. Effect of monoclonal antibodies divided by each type of drug compared with placebo by LBPI score changes from baseline.
Here and in Figs. 3–5: (▪) this square represents the individual studies effect. The square size varies to reflect the weight a particular study has in the overall analysis; (–) the black line represents the CIs of a study; (♦) the diamond represents the overall or summary effect. The outer edges of the diamond represent the CIs. IV — intravenously; SC — subcutaneously.

Results

Search results

We screened 2,443 records, and after removing duplicate studies, studies that are not related to mAb or CLBP, animal studies, non-randomised controlled trials, literature reviews, ineligible control, and reports without the full text, we screened article meeting inclusion criteria. Six clinical trials were included in this review study based on PRISMA algorithm (Fig. 1).

The studies included in this review were assessed according to the Jadad Scale, and all studies were deemed as high-quality studies (Table 2); thus, all studies were fit to be included in the review.

A total of six trials were included in the review, with 2223 participants in the mAb-group and 1628 in the control group. All included studies used a parallel-group double-blind design . All studies, except one, analysed the changes in LBPI and RMDQ scores as their primary outcome. Five out of six trials used nerve growth factor (NGF)-type mAb, and one study used receptor activator of nuclear factor-κB (NF-κB) ligand (RANKL).

Six trials evaluated the efficacy of mAb for CLBP using the decrease in LBPI score as its outcome. The summary of included studies is presented in Table 3, Appendicies 1 and 2. Of these, five trials were included in the meta-analysis comparing the efficacy of mAb to placebo in reducing LBPI score. Meta-analysis showed a result favouring the mAb-group in decreasing the LBPI score compared to placebo,

Agent; study	Dose, route of administration	Monoclonal antibody			Placebo			Weight, %	Std. mean difference; IV, fixed; 95% CI
		M	*m*	total	*M*	*m*	total		
Denosumab; Cai G. et al. (2018)	60 mg SC	–1.6	3.8168	31	–1.8	3.899	37	3.7	0.05; (–0.43)–0.53
	Subtotal			31			37	3.7	0.05; (–0.43)–0.53
	Heterogeneity: not applicable								
	Test for overall effect: Z = 0.21; $p = 0.83$								
Фасинумаб Fasinumab; Dakin P. et al. (2021)	6 mg SC every 4 weeks	–6	5.7	46	–3.8	4.5	46	4.9	–0.42; (–0.84)–(–0.01)
	9 mg SC every 4 weeks	–6.2	4.7	55	–3.8	4.5	46	5.3	–0.52; (–0.91)–(–0.12)
	9 mg SC every 8 weeks	–6.6	5.6	55	–3.8	4.5	46	5.3	–0.54; (–0.94)–(–0.14)
	Subtotal			156			138	15.4	–0.50; (–0.73)–(–0.26)
	Heterogeneity: $\chi^2 = 0.17$; df = 2 ($p = 0.92$); $I^2 = 0\%$								
	Test for overall effect: Z = 0.21 ($p = 0.83$)								
Tanezumab; Kivitz A.J. et al. (2013)	10 mg/kg IV every 8 weeks	–3.18	4.4656	295	–1.75	4.3981	230	27.8	–0.32; (–0.50)–(–0.15)
	20 mg/kg IV every 8 weeks	–2.8	4.4656	295	–1.75	4.3981	230	28.0	–0.24; (–0.41)–(–0.06)
	5 mg/kg IV every 8 weeks	–2.37	4.4171	232	–1.75	4.3981	230	25.1	–0.14; (–0.32)–(0.04)
	Subtotal			822			690	80.9	–0.24; (–0.34)–(–0.13)
	Heterogeneity: $\chi^2 = 1.99$; df = 2 ($p = 0.37$); $I^2 = 0\%$								
	Test for overall effect: Z = 4.55 ($p < 0.00001$)								
Total				**1009**			**856**	**100**	**–0.27; (–0.36)–(–0.17)**
Heterogeneity: $\chi^2 = 7.95$; df = 6 ($p = 0.24$); $I^2 = 25\%$									
Test for overall effect: Z = 5.69 ($p < 0.00001$)									
Test for subgroup differences: $\chi^2 = 5.78$; df = 2 ($p = 0.06$); $I^2 = 65.4\%$									

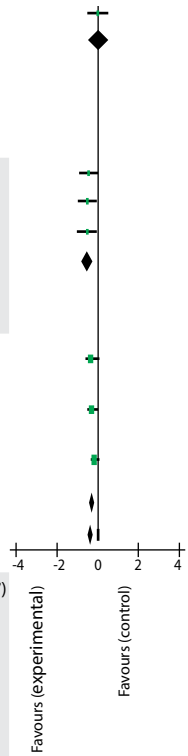

Fig. 3. Effect of monoclonal antibodies divided by each type of drug compared with placebo by RMDQ score changes from baseline.

with a statistically significant difference (weighted mean difference –0.23; 95% CI –0.31 to –0.15; $p \leqslant 0.001$), high certainty. However, the analysis revealed moderate heterogenicity (I^2 = 26%; fixed effects modelling). Subgroup analysis was done for each drug, and tanezumab showed a significant effect in lowering LBPI score (weighted mean difference of –0.29; 95% CI –0.39 to –0.19; $p \leqslant 0.001$) as well as fasinumab (weighted mean difference –0.24; 95% CI –0.47 to –0.02, p = 0.04). However, fulranumab showed a nonsignificant difference in lowering LBPI score, compared to placebo (weighted mean difference –0.02; 95% CI –0.18 to 0.13; p = 0.76; Fig. 2).

The meta-analysis included three trials to compare mAb efficacy using RMDQ scores. The analysis showed a result favouring the mAb-group in decreasing RMDQ score compared to placebo with significant difference (weighted mean difference –0.27; 95% CI –0.36 to –0.17; $p \leqslant 0.001$), high certainty. Nonetheless, low heterogeneity was found in the analysis with I2 25%. Subgroup analysis showed that fasinumab and tanezumab are significant in reducing RMDQ score (weighted mean difference –0.50; 95% CI –0.73 to –0.26 and weighted mean difference –0.24; 95% CI –0.34 to –0.13 respectively, both $p < 0.0001$; Fig. 3).

The most common adverse events reported in tanezumab group are arthralgia (128), nausea (108), and headache (90). However, in fasinumab group, arthralgia (52), headache (27), and nasopharyngitis (27) are the most frequent adverse events. In fulranumab group, back pain (47), arthralgia (46), and upper respiratory tract infection (45) are the most common adverse events. Unlike other mAb, denosumab only has a few adverse events. The most common adverse events are headache (10) and psychological effects (10), which we did not find in other drugs [10] (Table 4). Some studies defined serious adverse events as a condition requiring non-elective hospital admission and leading to deaths. The most common serious adverse events are musculoskeletal and connective tissue disorders requiring surgical management (femur fracture, patella fracture, intervertebral disc protrusion, and meniscus injury) [11, 12]. Other serious adverse events, although very rare, are represented by one case of haemorrhagic stroke in fasinumab 9 mg subcutaneously [12], lumbar radiculopathy (fulranumab 6 mg loading dose + 3 mg), peripheral neuropathy (fulranumab 10 mg) [13]. Other adverse events that occurred but the dose of tanezumab was not mentioned are headache, pneumonia, deep vein thrombosis and pulmonary embolism, with no deaths in that study [11].

Table 4. Adverse events with each agent

Agent (total patients with adverse events, *n*)*	Most common adverse events, *n* (%)	Least common adverse events
Tanezumab (954)	Headache 90 (9.43%); arthralgia 128 (13.41%); nausea 108 (11.32%); dizziness 55 (5.76%); parasthesia 93 (9.74%)	Back pain (4.08%); nasopharyngitis (4.50%); constipation (5.87%); upper respiratory tract infection (4.82%); neuralgia (0.1%); hyperesthesia (2.83%); hypoesthesia (2.51%); pain in extremity (4.71%); peripheral edema (2.20%)
Fasinumab (160)	Arthralgia, 52 (32.5%); headache, 27 (16.88%); nasopharyngitis, 27 (16.88%); paresthesia, 24 (15%); nausea, 12 (7.5%)	Dizziness (8.75%); hypoesthesia (8.75%); diarrhea (7.5%); pain in extremity (7.5%); urinary tract infection (6.88%); upper respiratory tract infection (5.63%); back pain (5.63%)
Fulranumab (259)	Back pain, 47 (18.15%); arthralgia, 46 (17.76%); upper respiratory tract infection, 45 (17.37%); paresthesia, 43 (16.60%); diarrhea 37 (14.29%); headache, 36 (13.9%); hypoesthesia, 34 (13.13%)	Pain in extremity (12.74%); sinusitis, (11.97%); nasopharyngitis (11.58%); edema peripheral (10.42%)
Denosumab (27)	Headache 10 (37%); phycological effects (malaise, insomnia, and depression), 10 (37%); musculoskeletal pain and stiffness (spasm), 9 (33.33%)	Flu-like (18.52%)

Note. *Each patient may have more than one adverse event.

Meta-analysis of six trials indicates that mAb have significantly greater odds of adverse events, favouring the placebo group (OR 1.23; 95% CI 1.06 to 1.43; $p = 0.007$). Moderate heterogenicity was found in the analysis with I^2 29% (Fig. 4). However, meta-analysis demonstrated no greater risk regarding the serious adverse events in mAb vs. placebo with OR 1.00 (95% CI 0.69 to 1.46; $p = 0.98$; Fig. 5).

Risk of bias of the included studies

The risk of bias assessment was low in a few trials: random sequence generation ($n = 3$; 50%), allocation concealment ($n = 3$; 50%), blinding of participants and personnel ($n = 6$; 100%), blinding of outcome assessment ($n = 5$; 83%), incomplete data ($n = 4$; 67%), selective reporting ($n = 6$; 100%), other bias ($n = 2$; 33%; Table 5).

DISCUSSION

Efficacy

This systematic review and meta-analysis evaluated the efficacy and safety of mAb for CLBP. mAb significantly improve the intensity of pain scale and disability as shown by the LBPI and RMDQ scores, compared to placebo.

Agent; study	Dose, route of administration	Monoclonal antibody		Placebo		Weight, %	Odds ratio (M–H, random); 95% CI
		events	total	events	total		
Denosumab; Cai G. et al. (2018)	60 mg SC	27	31	25	37	1.4	3.24; 0.92–11.37
Fasinumab; Dakin P. et al. (2021)	6 mg SC every 4 weeks	41	139	52	140	6.8	0.71; 0.43–1.17
	9 mg SC every 4 weeks	63	139	52	140	7.3	1.40; 0.87–2.26
	9 mg SC every 8 weeks	56	140	52	140	7.2	1.13; 0.70–1.83
Tanezumab; Katz N. et al. (2011)	20 µg/kg IV once	50	88	27	41	3.4	0.68; 0.32–1.48
Tanezumab; Kivitz A.J. et al. (2013)	10 mg/kg IV every 8 weeks	171	295	120	230	11.1	1.26; 0.89–1.79
	20 mg/kg IV every 8 weeks	190	295	120	230	11.0	1.66; 1.17–2.36
	5 mg/kg IV every 8 weeks	141	232	120	230	10.3	1.42; 0.98–2.05
Tanezumab; Markman J.D. et al. (2020)	10 mg	211	407	189	409	14.3	1.25; 0.95–1.65
	5 mg	191	407	189	409	14.2	1.03; 0.78–1.38
Fulranumab; Sanga P. et al. (2016)	10 mg SC every 4 weeks	66	86	58	76	3.7	1.02; 0.49–2.12
	1 mg SC every 4 weeks	59	77	58	76	3.6	1.02; 0.48–2.15
	3 mg SC every 4 weeks	64	77	58	76	3.2	1.53; 0.69–3.39
	6 mg LD + 3 mg SC every 4 weeks	70	78	58	76	2.5	2.72; 1.10–6.70
Total			**2491**		**2310**	**100.0**	**1.23; 1.06–1.43**
Total events		1400		1178			
Heterogeneity: $Tau^2 = 0.02$; $\chi^2 = 18.37$; df = 13 ($p = 0.14$); $I^2 = 29\%$							
Test for subgroup differences: Z = 2.69 ($p = 0.007$)							

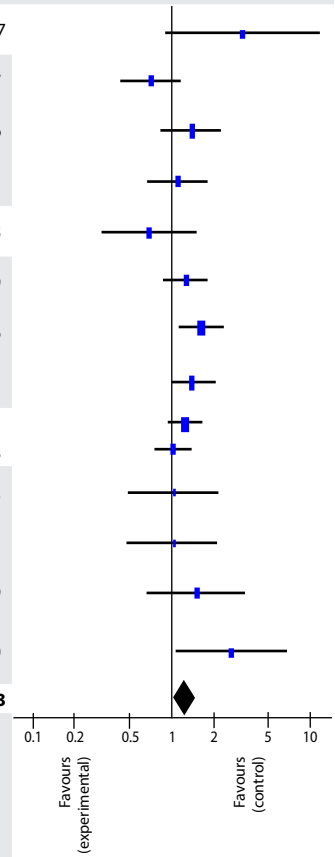

Fig. 4. Adverse events (safety) of monoclonal antibody compared to placebo for CLBP.

Tanezumab is a humanised IgG2-mAb that inhibits NGF by activating trkA receptors on nociceptive neurons. This inhibition of NGF affects both acute and chronic painful states, thereby acting as a novel mechanism of action, unlike opioids and nonsteroidal anti-inflammatory drugs. Tanezumab interferes with pain signals produced by skin, muscles, and organs precluding them from reaching the central nervous system. In our study tanezumab showed a significant effect in lowering LBPI and RMDQ scores. Tanezumab was first indicated for treating moderate to severe chronic osteoarthritic pain of the hip and knee joint and CLBP. One study by Brown et al. found that tanezumab is superior in providing pain relief and improved physical function and patient's global assessment compared to placebo in painful hip arthritis [14]. Other clinical trials investigate the role of NGF inhibition in neuropathic conditions. The study by C. Bramson et al. found that tanezumab provided effective pain relief in patients with diabetic peripheral neuropathy. It is also found to cause pain reduction in postherpetic neuralgia patients but at higher doses, although the results were insignificant [15]. Common adverse events observed in previous tanezumab studies were peripheral sensations such as paresthesia and hypoesthesia followed by headache, arthralgia, extremity pain, urinary tract infection, and upper respiratory tract infection. The list of adverse events was consistent with the result of this study.

Fasinumab 6 mg subcutaneously, 9 mg subcutaneously, and 9 mg intravenously significantly improved pain intensity and disability, as shown by the LBPI and RMDQ scores. Fasinumab has also been used in other diseases to decrease joint pain and improve physical function in hip or knee osteoarthritis patients [16]. Our study found that fasinumab is generally well tolerated, similar to the previous research [16].

Our study found that all doses of fulranumab did not significantly improve LBPI scores. A study by A.J. Mayorga et al. compared fulranumab, placebo, and oxycodone

Agent; study	Dose, route of administration	Monoclonal antibody events	Monoclonal antibody total	Placebo events	Placebo total	Weight, %	Odds ratio (M–H, random); 95% CI
Denosumab; Cai G. et al. (2018)	60 mg SC	0	31	2	37	1.5	0.23; 0.01–4.88
Fasinumab; Dakin P. et al. (2021)	Combined	10	418	4	140	10.1	0.83; 0.26–2.70
Tanezumab; Katz N. et al. (2011)	20 µg/kg IV once	0	88	0	41		Not accessed
Tanezumab; Kivitz A.J. et al. (2013)	10 mg/kg IV every 8 weeks	3	295	5	230	6.7	0.46; 0.11–1.96
	20 mg/kg IV every 8 weeks	3	295	5	230	6.7	0.46; 0.11–1.96
	5 mg/kg IV every 8 weeks	4	232	5	230	7.9	0.79; 0.21–2.98
Tanezumab; Markman J.D. et al. (2020)	10 mg	7	407	4	409	9.2	1.77; 0.51–6.10
	5 mg	6	407	4	409	8.7	1.51; 0.42–5.41
Fulranumab; Sanga P. et al. (2016)	10 mg SC every 4 weeks	7	77	7	76	11.6	0.99; 0.33–2.96
	1 mg SC every 4 weeks	9	77	7	76	12.9	1.30; 0.46–3.70
	3 mg SC every 4 weeks	6	77	7	76	10.8	0.83; 0.27–2.60
	6 mg LD + 3 mg SC every 4 weeks	11	78	7	76	13.9	1.62; 0.59–4.42
Total			**2482**		**2330**	**100.0**	**1.00; 0.69–1.46**
Total events		66		57			
Heterogeneity: $Tau^2 = 0.00$; $\chi^2 = 5.78$; df = 10 ($p = 0.83$); $I^2 = 0\%$							
Test for overall effect: Z = 0.02 ($p = 0.98$)							

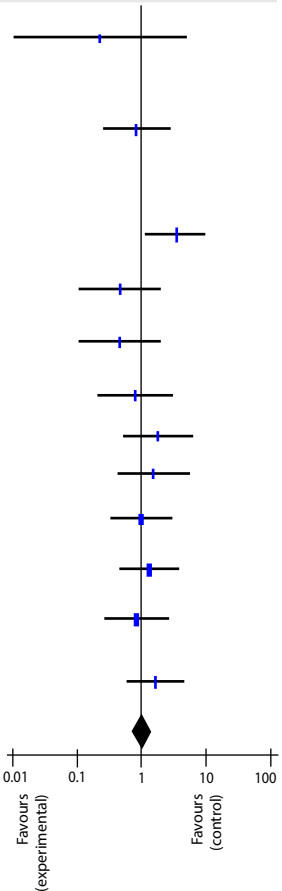

Fig. 5. Serious adverse events (safety) of monoclonal antibody compared to placebo for CLBP.

to find that responder rates were significantly greater in the fulranumab groups compared with the oxycodone group, but no significant differences in responder rates were observed between the two fulranumab groups and placebo groups [18]. However, at that time, the FDA held all anti-NGF trials [17, 18]. Nonetheless, data from patients who did not withdraw show that the oxycodone group had a greater discontinuation rate because of treatment-emergent adverse events compared to fulranumab and placebo groups. Fulranumab at all doses showed minimal adverse events and was mainly well tolerated, which parallels other studies [17, 18].

The humanised mAb is one for which both chain types are humanised due to antibody engineering. A humanised chain is typically one in which the complementarity determining regions of the variable domains are foreign, originating from one species other than human or synthetic. In contrast, the remainder of the chain is of human origin. Humanisation assessment is based on the resulting amino acid sequence and not on the methodology that allows protocols other than grafting. The variable domain of a humanised chain has a V region amino acid sequence, which, analysed as a whole, is closer to humans than other species [19]. Humanized mAb are created by grafting the murine hypervariable regions of the light and heavy chains onto a human antibody framework. This results in molecules that are approximately 95% human [20]. Human mAb (fulranumab and fasinumab) are mAb created using animals carrying human Ig genes. These transgenes include parts of the variable regions, which enable the recombination of the human antibodies and inactivated endogenous Ig genes in animals, thus generating fully human mAb.

MAb focusing on particular cytokines involved in the amplification and transmission of pain sensation in chronic low back pain (CLBP) have primarily targeted inflammatory processes associated with NGF and TNF cytokines [6]. Tanezumab, fasinumab and fulranumab are mAb that target NGF, a pleiotropic neurotrophin that plays significant role in generation and maintaining both nociceptive and neuropathic pain. NGF also contribute to chronic pain [3]. Expression of NGF has been found to occur early in

Table 5. GRADE Assessment

No. of studies	Certainty assessment: study design	risk of bias	inconsistency	indirectness	imprecision	considerations	No. of patients: antibody	placebo	Effect, absolute (95% CI)	Certainty
LBPI changes										
12	Randomised trials	Not serious	Serious	Not serious	Not serious	—	1409	1219	< **1.48**; (< 2.63)–(< 0.33)	⊕⊕⊕◯ High
RMDQ changes										
7	Randomised trials	Not serious	Serious	Not serious	Not serious	—	1009	865	< **1.81** (< 3.2)–(< 0.41)	⊕⊕⊕◯ High

response to inflammatory mediators such as interleukin one and TNFα involved in neurogenic pain transmission [21]. Moreover, NGF is involved in peripheral sensitisation and then sensitises nociceptive neurons to painful stimuli through upregulation of ion channels and receptors present on primary afferent nerve fibres and increases the release of pain mediators that potentiate the pain response such as substance P [3, 22]. Currently, studies on the effect of infliximab that targets TNF on CLBP are in progress [23]. Future results may add more information regarding the best mAb to address chronic back pain.

One study used denosumab targeting RANKL as the choice of mAb. Denosumab showed a significant improvement in reducing LBPI score but not substantial for RDMQ score. Another prospective cohort study assessing denosumab's effectiveness for back pain in post-menopausal women showed a significant effect [24]. None of the fatal or life-threatening adverse events were shown in this study and the previous one [25].

Denosumab is the most potent anti-resorptive agent and a fully human igG2-mAb that neutralises RANKL, blocking the interaction between the cytokine and its receptor (RANK), with consequent inhibition of osteoclast-mediated bone resorption [26]. Denosumab can reduce bone pain through several mechanisms. Denosumab lowers osteoclast-mediated acidification by negatively modulating the NF-κB by inhibiting the RANK/RANKL pathway and delaying the pain catastrophising response [27].

Safety

The safety profile of mAb is parallel with previous studies [15–18, 25]. Although the mAb group reported more adverse events, none were life-threatening or led to death. mAb had no greater risk regarding serious adverse events than placebo. Dakin et al. reported one patient from fasinumab 6 mg group with a history of smoking who died of small cell lung cancer during the post-treatment follow-up period. The event was considered unrelated to the study drug [12]. P. Sanga et al. also reported one patient from fulranumab 10 mg group who died due to streptococcal pneumonia and malignant lung neoplasm [13] J.D. Markman et al. reported 7 deaths during the study (56-week treatment period and 24-week follow-up period) [28]. However, none of those deaths (cardiac failure, road traffic accident, myocardial infarction and aneurysmal rupture, influenza and toxicity to multiple agents, i.e. cocaine, heroin, and fentanyl) was considered to be treatment-related by investigators.

Application

The potential of mAb agents in this study, like tanezumab, fulranumab, fasinumab, and denosumab, to inhibit or block crucial steps in the generation and exaggera-

tion of pain and inflammation suggests that these drugs could have a adjunctive role in the management of CLBP where traditional therapy and interventions have failed to provide improvement and adequate relief for patients. In studies that we included, mAb therapy can be prescribed in moderate-to-severe axial predominant CLBP (primary location between the 12th thoracic vertebra and lower gluteal folds, with or without radiation into the posterior thigh) of ⩾ 3 months in adult patients ⩾ 18 years, average LBPI score ⩾ 5 (on an 11-point numeric rating scale, NRS) and history of inadequate response to ⩾ 3 different categories of standard of care analgesics [13, 28]. Other conditions that we found that can be treated with mAb are non-radiculopathy CLBP, with the primary pain location between the 12th thoracic vertebra and lower gluteal folds, use of analgesic medications for > 4 days per week over the month, average LBPI score of ⩾ 4 using an 11-point NRS over the previous 24 hours at screening while on current treatment [10–11, 29].

Strength and weakness

To our knowledge, this study is the first to analyse the efficacy of mAb regardless of their mechanism of action in CLBP. This meta-analysis has low to moderate heterogeneity based on the I2 value, which can be the strength of this study. Nonetheless, this result should be seen in the light of a few limitations. Data regarding the efficacy of each drug, especially denosumab, were minimal due to limited studies. The definition of serious adverse events in this study may vary as we defined it based on each trial. Nonetheless, CLBP is a diverse condition arising from various factors, including degenerative spinal changes and central brain structure dysfunction. A significant portion of the participants have likely experienced primary CLBP due to central sensitization. Unfortunately, this aspect could not be explored in greater depth in this review, representing one of its limitations. Despite these limitations, our study included more than 2,000 patients receiving mAb; thus, it is considered an extensive analysis to compare the mAb efficacy.

Conclusion

This systematic review and meta-analysis found that mAb had a favourable effect in reducing LBPI and RMDQ scores compared to the placebo group, with relatively safe adverse events profile under short-term surveillance. This effect may depend on the types of drugs used, with tanezumab and fasinumab as drugs that reduced both LBPI and RMDQ scores significantly.

Additionals to the article:

Appendix 1. Summary of the studies included.

DOI: https://doi.org/10.17816/ACEN.1027-31629

Appendix 2. Summary of primary and secondary end-points of the studies included.

DOI: https://doi.org/10.17816/ACEN.1027-31630

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