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Review article

Infliximab, methotrexate and their combination for the treatment of rheumatoid arthritis: a systematic review and meta-analysis☆

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ABSTRACT

We performed a systematic review to evaluate the efficacy and safety of infliximab + methotrexate (IFX + MTX) regimens versus MTX alone or in combination with other disease-modifying anti-rheumatic drugs (DMARDs). We searched through major databases, the grey literature and did a manual search. Two independent reviewers conducted the selection, data extraction and analysis of the quality of the studies. Meta-analysis was conducted using Review Manager® 5.1 software. Nine trials were included. The mean modified Jadad score was 4.4, but only one study showed low risk of bias. IFX + MTX regimen presented better responses in clinical outcomes of ACR and DAS28 by up to 54 weeks, and of radiographic progression by up to 104 weeks. Withdrawals due to lack of efficacy was lower in the IFX + MTX group. No significant difference in adverse events was observed. The IFX + MTX combination is more effective than treatment with MTX alone or DMARDs combination. This regimen presented good tolerability in patients previously treated with DMARDs, not treated with MTX or with insufficient responses to MTX. The efficacy of IFX + MTX is noted primarily during initial periods of treatment. High doses of IFX were as effective as the standard dose, but with possible higher risk of serious infections. Therefore, we advise clinicians to use the standard dose of IFX 3 mg/kg every 8 weeks.

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Infliximabe, metotrexato e sua combinação no tratamento da artrite reumatoide: revisão sistemática e metanálise

Palavras-chave:
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RESUMO

Foi feita uma revisão sistemática para avaliar a eficácia e a segurança do esquema infliximabe + metotrexato (IFX + MTX) *versus* MTX isoladamente ou em combinação com outros medicamentos modificadores do curso da doença (MMCD). Pesquisou-se nas principais bases de dados eletrônicas e na literatura cinzenta e fez-se uma busca manual. Dois revisores independentes fizeram a seleção, extração de dados e análise da qualidade dos estudos. A metanálise foi feita com o software Review Manager® 5.1. Incluíram-se nove estudos. O escore médio na escala de Jadad modificada foi de 4,4, mas somente um estudo mostrou baixo risco de viés. O esquema IFX + MTX apresentou melhores respostas nos desfechos clínicos do escore ACR e do DAS28 por até 54 semanas e na progressão radiográfica por até 104 semanas. Os abandonos decorrentes da falta de eficácia foram menores no grupo IFX + MTX. Não foi observada diferença estatisticamente significante nos eventos adversos. A combinação IFX + MTX é mais eficaz do que o tratamento com MTX isolado ou em combinação com MMCD. Esse esquema apresentou boa tolerabilidade em pacientes previamente tratados com MMCD, não tratados com MTX ou com respostas insuficientes ao MTX. A eficácia do regime IFX + MTX é observada principalmente durante os períodos iniciais do tratamento. Altas doses de IFX foram tão eficazes quanto a dose padrão, mas com a possibilidade de "um" maior risco de infecções graves. Recomenda-se, portanto, que os médicos utilizem a dose padrão de IFX de 3 mg/kg a cada oito semanas.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterised by peripheral, symmetric polyarthritis with potential for joint deformity that can cause functional disability, premature mortality and reduced quality of life. It is estimated that 0.3–1.0% of the population worldwide is affected by RA, which is most frequently observed in developing countries and in women.[1]

The treatment of RA patients combines educational, preventive and non-pharmacological interventions with pharmacological treatment and surgical procedures. First-line therapy includes the early use of a synthetic disease-modifying anti-rheumatic drug (DMARD), such as methotrexate (MTX), which is the drug of choice.[2] However, only 20–40% MTX monotherapy-treated patients show a satisfactory clinical response.[3] Drug combinations are a valid strategy in non-responsive patients, which may include the addition of another synthetic DMARD or the biological DMARD agents, such as tumour necrosis factor α blockers (anti-TNFα).[4] Infliximab (IFX) is a chimeric monoclonal antibody (murine) of the anti-TNFα class that represents approximately 40% of biological agent prescriptions.[5,6]

Second-line treatment strategies show similar rates of success and the choice among them is based primarily on the presence or absence of a poor prognosis and in the disease activity.[4,7] The benefits of adding sulfasalazine (SSZ) and hydroxychloroquine (HCQ),[8–11] leflunomide[12] or cyclosporin[13] to MTX therapy have been demonstrated. The IFX + MTX combination has been assessed in numerous systematic reviews[14–19] but their control groups included only placebo or MTX treatment. Key issues, including the effect of disease duration, dose and patient profile, were not sufficiently addressed in most of these reviews.

With this systematic review and meta-analysis we aimed to assess the efficacy and safety of IFX + MTX compared to MTX in monotherapy or in combination with other synthetic DMARDs considering treatment-relevant clinical outcomes.

Methods

A systematic review with meta-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions. The results were reported according to the "Preferred Reporting Items for Systematic Reviews and Meta Analyses: The PRISMA statement".[20] This review is part of another project entitled "Evaluation of the effectiveness and safety of biological agents adalimumab, etanercept, infliximab and rituximab used in the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, Brazil and Minas Gerais", which was performed by the Research Group on Pharmacoepidemiology and Research Group on Health Economics at the UFMG.

Search strategy

The online search was performed in EMBASE (until April 2012), CENTRAL (until June 2012), PubMed (until July 2012) and LILACS (until October 2012) databases. Different combinations of keywords, mesh terms and filters were applied, and the full search strategy for each database was provided online in Appendix 1. We performed a manual search in the