EVIDENCE BRIEF

Combination therapy for rheumatoid arthritis

(DCP4 ID: MSKD01-01)
Cluster: Musculoskeletal

FairChoices
DCP Analytic Tool

Combination therapy, including low-dose corticosteroids and generic disease-modifying antirheumatic drugs (including methotrexate), for individuals with moderate to severe rheumatoid arthritis

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Description of condition and intervention

Rheumatoid arthritis (RA) is a chronic inflammatory disorder of unknown aetiology that involves synovial joints. The arthritis may affect the activities of daily living like walking, climbing stairs, dressing, doors, use of a toilet and cause significant locomotor disability in patients unresponsive to treatment. Much variation is seen in the patterns of RA at individual level. Initial treatment of RA targets to reduce the joint damage. For this, disease modifying antirheumatic drugs (DMARDS) like methotrexate (MTX) may be indicated either alone or in combination with other drugs for the tight control of the active disease. (Source: UpToDate accessed on August 28, 2021.) Thus treatment regimens may vary including anti-inflammatory drugs (NSAIDs), glucocorticoids, traditional DMARDs (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, cyclosporine) and biologic DMARDs *(*Singh JA et al. 2013*)*.

According to meta-analyses, biologic DMARDs that is combined with MTX are more effective compared to MTX alone for controlling the disease. In addition to that, the meta-analysis study that includes 158 trials showed triple therapy (methotrexate+sulfasalazine+hydroxycholoroquine) was also superior to MTX alone, but not statisticcally different from MTX + biologic DMARD. However, triple therapy and combined biologic DMARDs with methotrexate were found effective to controll RA disease activity (H*azlewood et al. 2016)*. In this evidence brief, we present the effect and cost of the following intervention being analysed in FairChoices:DCP Analytical tool:

Combination therapy, including low-dose corticosteroids and generic disease-modifying antirheumatic drugs (including methotrexate), for individuals with moderate to severe rheumatoid arthritis

International guidelines

Organization	Indications/recommendations	Applicability in LIC & Lower MIC settings
BMJ NICE guideline updated in 2020	**1.** Initial pharmacological management Conventional disease-modifying anti-rheumatic drugs 1.1. For adults with newly diagnosed active RA: - First line treatment with cDMARD (conventional disease-modifying antirheumatic drugs) monotherapy using oral metothrexate, leflunomide or sulfasalazine as soon as possible (ideally within 3 months of onset of persistent symptoms). - Consider hydroxychloroquine for first-line treatment as an alternative to oral methotrexate, leflunomide or sulfasalazine for mild or palindromic disease. 1.2. Consider short-term bridging treatment with glucocorticoids (oral, intramuscular or intra-articular) when starting a new cDMARD (2018) 1.3. Offer additional cDMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation. [2018] **2.** Further pharmacological management Biological and targeted synthetic DMARDs 2.1. Anakinra is not recommended for the treatment of RA. 2.2. Patients currently receiving anakinra for RA should continue therapy with anakinra until they and their consultant consider it is appropriate to stop. Glucocorticoids 2.3. Offer short-term treatment with glucocorticoids for managing flares in adults with recent-onset or established disease to rapidly decrease inflammation. 2.4. In adults with established RA, only continue long-term treatment with glucocorticoids when:	

	- the long-term complications of glucocorticoid therapy have been fully discussed all other treatment options (including biological and targeted synthetic DMARDs) have been offered (2009, amended 2018).	

Intervention attributes

Type of interventions

Chronic management care

Delivery platform

This intervention may be delivered at first –level hospital.

Equity

In addition to considerations like cost-effectiveness and health systems factors, dimensions of equity can be relevant for priority setting. The opportunity for a long and healthy life varies according to the severity of a health condition that individuals might have, so there are inequities in individuals' opportunities for long and healthy lives based on the health conditions they face. Metrics used to estimate the severity of illness at an individual level can be used to help prioritize those with less opportunity for lifetime health. FairChoices: DCP Analytics Tool uses Health adjusted age of death (HAAD), which is a metric that estimates the number of years lived from birth to death, discounting years lived with disability. A high HAAD thus represents a disease less severe in terms of lifetime health loss, while a low HAAD represents a disease that is severe on average, causing early death or a long period of severe disability. It is also possible to estimate the distribution of HAAD across individuals with a health condition. FairChoices shows for each intervention an average HAAD value of the conditions that are affected by respective interventions that have health effects. Additionally, a plot shows HAAD values for around 290 conditions (Johansson KA et al 2020).

Time dependence

Moderate level of urgency. Treatment outcomes not highly affected by some days of delay.

Population in need of interventions

Treated population: All the prevalent cases (aged 16 to 99 years) are the treated population for receiving combination therapy including low-dose corticosteroids and generic disease-modifying antirheumatic drugs (including methotrexate). The treated fraction is assumed 100% for receiving this intervention. Rheumatoid arthritis in 16 years and younger is classified as juvenile arthritis (Huizinga et al 2011).

Disease state addressed

This intervention targets rheumatoid arthritis.

Intervention effect and safety

Table 1: Effect and safety of treatment for rheumatoid arthritis

Effect of intervention		Certainty of evidence
Mortality (due to condition)	In a study by Rodriguez et al 2016, the mortality risk/1000 patient-years for biologics was 12.6(6-26), for DMARDs was 22.3(18.4-27.1), and for those without treatment was 89.1. Significantly lower mortality was observed in patients treated with rituximab (HR adj=0.57 (95% CI 0.39 to 0.84) compared to those receiving methotrexate (Listing et al 2015). Therefore, mortality reduction is estimated as (89.1-22.3)/89.1=0.75	See appendix
Disability	In a cost-effectiveness analysis, the mean disability index measured by HAQ-DI was reported to be significantly reduced from 1.43 ± 0.71 to 0.81 ± 0.61, p < 0.001, after 3 months treatment on synthetic DMARDS. In another study by Gaujoux-Viala 2010, methotrexate was found to be more efficacious in the reduction of signs and symptoms, disability and radiographic	

	structural damage when compared to other synthetic DMARDs. About 85% of patients in disease remission had HAQ scores below 0.50. In those with no remission, HAQ scores were high and only 18% had HAQ scores <0.50 on one or more occasions (Gullick et al 2019).	

Model assumptions

Table 2: Summary of model parameters and values used in FairChoices – DCP Analytical Tool

Category	Model parameter	Notes
Intervention	Combination therapy, including low-dose corticosteroids and generic disease-modifying antirheumatic drugs (including methotrexate), for individuals with moderate to severe rheumatoid arthritis	
Cost parameters		
Treated population	Based on prevalence of rheumatoid arthritis	Global Burden of Disease Study 2019
Gender	Both male & female	
Age	16-99 years	
Treated fraction	1	
Effect parameters		
Affected population	Those with condition	
Affected gender	Both male & female	
Affected fraction age	16 to 99 years	
Affected fraction	Those with condition	

Comparison	No intervention	
Mortality Reduction (RRR)	0.75	Rodriguez et al 2016
Disability Reduction (RRR)	0.43	Gaujoux-Viala 2010

Intervention cost

For individuals with moderate to severe rheumatoid arthritis, the cost of combination therapy, including low-dose corticosteroids and generic disease-modifying antirheumatic drugs (including Methotrexate), is estimated at USD 84.15 per person-year in specified population in LIC in 2016 (DCP volume 9). The unit cost estimate was developed based on the cost for Methotrexate ($0.15 *52 days), Prednisone ($0.08*1year) and, Hydroxychloroquine ($0.08* 1 year). An additional $10 was added to the medication cost to estimate the cost of 30 mins level 4 provider time and tests. The medication costs were derived from the World Health Organization's "Essential Medicines and Health Products Information Portal."

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DCP Volume 9 available at https://openknowledge.worldbank.org/bitstream/handle/10986/28877/9781464805271.pdf?sequence=2&isAllowed=y

WHO Essential Medicines and Health Products Information Portal available at https://digicollections.net/medicinedocs/#p/home

Appendix

Literature Review for effectiveness & safety

This literature search is an example of Level 1 search for intervention inputs taken from DCP3 or generated in an ad hoc manner (e.g., quick google search found one study of cervical cancer screening cost-effectiveness that was used to create an effectiveness parameter for that intervention).

Treated population:

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Both male and female

Age 16 years and above

Treatment for all with the diagnosis – incident and prevalent cases

1st line Methotrexate – if no contraindications/side effects/planning to conceive – 90%**

2nd line Hydroxychloroquine – either as an alternative to methotrexate or as add on therapy 10%**

Folic acid for all patients on methotrexate – 90% of patients ** (Smolen et al 2013)

Prednisolone for patients with disease flares/high disease activity -56% (Batko B 2019)

Calcium supplements – when patient on steroids for ≥ 1 month – 56%

3rd line Rituximab – for patients who don't respond to the combination therapy – 18% – this will still be used in conjunction with methotrexate as combination is more effective than monotherapy (Nam JL et al 2017)

Joint injections for patients with persistent single/few joint pains

** from ongoing study finding 10% could not use methotrexate because of wishes to conceive no adverse events reported (yet) but these can be expected with increasing doses

Notes:

Community education on rheumatoid arthritis, encouraging active lifestyle to decrease obesity and cessation of smoking.

Consider investigations required for diagnosis and follow up.

Non-steroidal drugs that may be needed on and off when patient has a flare their consumption decreases when patient's disease is controlled

Consider before rituximab injection patients will need hepatitis B and C treatment (if positive), pneumococcal vaccine, co-trimoxazole (septrin) for prophylaxis and isoniazid preventive therapy against latent tuberculosis so will require additional investigations and drugs

Level of evidence of efficacy studies:

1. low (expert opinions, case series, reports, low-quality case control studies)
2. moderate (high quality case control studies, low quality cohort studies)
3. high (high quality cohort studies, individual RCTs)
4. very high (multiple RCTs, metaanalysis, systematic review, clinical practice guidelines)

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