Review

Monotherapy is a relevant option in rheumatoid arthritis treatment: a literature review

A. Doria¹, D. Zavaglia²

¹Rheumatology Unit, Department of Medicine, University of Padova, Italy; ²Medical Department, Pfizer Italia, Roma, Italy.

Andrea Doria, MD, PhD
Daniela Zavaglia, MD

Please address correspondence and reprint requests to:
Dr Andrea Doria,
Division of Rheumatology,
University of Padova,
Via Giustiniani 2,
35128 Padova, Italy.
E-mail: adoria@unipd.it

Received on June 8, 2018; accepted in revised form on October 8, 2018.

Key words: rheumatoid arthritis treatment, monotherapy, combination therapy, biological DMARD, conventional synthetic DMARD, targeted synthetic DMARD, Jak-inhibitors

ABSTRACT

The latest revision of the European League Against Rheumatism (EULAR) recommendations for rheumatoid arthritis (RA) treatment maintains the indication for the combined therapy of biological disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), namely Jak-inhibitors as tofacitinib and baricitinib, with conventional synthetic DMARDs (csDMARDs). Moreover, the use of bDMARDs and tsDMARDs should be restricted to patients who failed to achieve an adequate response to one or more csDMARDs, in accordance with the current evidence showing the superiority of combination therapy over monotherapy. In patients who cannot use csDMARDs as comedication, IL-6 inhibitors and tsDMARDs should be preferred to other bDMARDs because they are apparently more effective as monotherapy. Registry and real-world data demonstrate that monotherapy is far more commonly used than expected based on treatment recommendations, currently being about 30% of patients with RA on bDMARD monotherapy. We review here the literature on most commonly used DMARDs in monotherapy for RA. Our review points at an increasing evidence of the potential of some bDMARDs and tsDMARDs in monotherapy, which may become a considerable and realistic option in RA patients.

Introduction

Rheumatoid arthritis (RA) is the most common form of immune-mediated inflammatory diseases, affecting 0.5–1.0% of the general population, and being associated with significant morbidity and disability. The latest European League Against Rheumatism (EULAR) recommendations for RA treatment confirm that methotrexate (MTX) should be used either alone or in combination with another conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) as first-line treatment, before adding any biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs). The new edition of the recommendations extends indeed possible additional treatments to tsDMARDs, following the new data on their safety and effectiveness that were published after the previous edition and even suggest some possible advantages of tsDMARDs compared with bDMARDs. Moreover, despite previous reports showing that the combination of a bDMARD with a csDMARD was more effective than bDMARD monotherapy, new evidence has been shown on somewhat better efficacy of tocilizumab monotherapy, and – more convincingly – of Jak-inhibitors monotherapy, on signs and symptoms, physical function and joint damage, compared with MTX. However, data from European and USA registries and other real-world data show that the use of bDMARDs in monotherapy is far more common than expected on the basis of treatment recommendations because about 30% of patients with RA are actually on bDMARD monotherapy. The concomitant treatment with MTX (but not with other csDMARDs) improved clinical response: 6-month DAS28 remission was 51% in the case of combination with MTX, 41% in monotherapy and 39% in patients taking a csDMARD other than MTX (21).

Competing interests: medical writing and editorial support were provided by CDM and TBWA and were funded by Pfizer. A. Doria received an honorarium from Pfizer in connection with the development of this manuscript.
D. Zavaglia is a Pfizer employee.
This may be due to different patients’ selection and different patients’ compliance in RCTs and to real-life settings. The unexpectedly high prevalence of bDMARD monotherapy has been attributed mainly to low tolerability and poor adherence to MTX. Catay et al. reported that the use of biologics in monotherapy is due to medical prescription in 60% of cases and to lack of patients’ compliance in the remaining 40% of cases. Adherence to therapy may be influenced by several factors: e.g. treatment regimens including more medications are associated with an increase in the risk of poor adherence and poor persistence in therapy compared with monotherapy regimens.

The above considerations make the possibility of achieving effective monotherapy an appealing option for patients with RA. Reasons for preferring monotherapy may include the possibility of reducing adverse effects, improving compliance, avoiding drug-drug interactions, overcoming inadequate pharmacological clearance in elderly patients, as well as the patient’s preference. Quite a few clinical studies have specifically investigated the efficacy of bDMARDs monotherapy, showing rather encouraging results. As anticipated above, the efficacy of tsDMARDs, such as tocetinib and baricitinib, was shown when administered as monotherapy, entering tsDMARDs into the therapeutic armamentarium of RA, with the indication for the use after failure of at least one csDMARD. This paper reviewed RCTs, data from registers, summaries of biological monotherapies, and recommendations, with the aim to clarify the current role of monotherapy approach in RA.

**Methotrexate**

MTX remains the mainstream of RA treatment. According to the current European recommendations, MTX should be used as part of the first-line RA strategy and it should be maintained in combination with a bDMARD or tsDMARD if the treatment target is not achieved after 6 months. Factors predicting the efficacy of MTX monotherapy in patients with RA have been identified in male gender, low disease activity, low level of matrix metalloproteinase and lack of previous DMARD use. Since TNFis have been introduced in the late 90s, MTX use has gradually switched in the clinical practice, toward a more rapid addition of bDMARDs and an earlier MTX withdrawal.

A meta-analysis of 7 trials on overall 732 patients with RA evaluated the short-term effects of MTX monotherapy compared with placebo. At 52 weeks, MTX monotherapy significantly improved the American College of Rheumatology (ACR) 50 response, physical function, Short-Form-36 (SF-36) physical component, but not radiographic scores. The discontinuation rate due to adverse events (AEs) was 16%.

Table I summarises the main results obtained with MTX in monotherapy compared to placebo or combined with other DMARDs.

**MTX in monotherapy versus other csDMARDs**

A recent Cochrane meta-analysis compared the efficacy of MTX in monotherapy and in combination with other DMARDs in patients with RA either MTX-naïve or with insufficient response to MTX (MTX-IR). MTX-based combinations resulted significantly more effective than MTX monotherapy in terms of ACR50 response, but not in terms of radiographic progression inhibition either in MTX-naïve patients or in MTX-IR.

In patients with early RA who are nonresponders to MTX in monotherapy (Swefot trial), the addition of sulfasalazine and hydroxychloroquine achieved a good response according to EU-LAR criteria in 25% of patients at 12 months. In the tREACH trial, comparing 3 treatment groups, one receiving MTX monotherapy and the other two receiving MTX in combination with other csDMARDs (sulfasalazine and hydroxychloroquine) and either oral or intramuscular glucocorticoids, disease activity, radiographic progression and functional ability were similar in all 3 groups. In the CareRA trial, in patients with early RA and predictors of aggressive disease, the combination of MTX with other csDMARDs was not superior to MTX monotherapy (both arms were combined with glucocorticoids).

In addition, more recent RCTs, as reviewed by Chatzidionysiou et al, are consistent with these results showing that combination of csDMARDs is not more effective than MTX monotherapy.

**MTX in monotherapy versus bDMARDs**

In the Cochrane meta-analysis mentioned before, MTX combined with bDMARDs (TNFis, abatacept, rituximab, and tocilizumab) was superior to MTX alone in terms of ACR50 response in MTX-naïve and in MTX-IR patients, and in terms of radiographic progression inhibition only in MTX-naïve patients.

In the RADIUS (Rheumatoid Arthritis DMARD Intervention and Utilization Study) including 2 observational registries of over 10 000 patients who required a change in their existing RA treatment regimen (switch to or addition of a new DMARD), after one-year therapy, etanercept alone or combined with MTX was more likely to obtain an ACR20 response than MTX alone, while no difference was observed between MTX alone or combined with infliximab or with other csDMARDs. In the COMET trial, in which the population of the study was MTX naïve, MTX in monotherapy induced less clinical remission and more Rx progression than in combination with etanercept. In a study comparing etanercept and MTX monotherapies in patients with early RA and never treated with MTX, etanercept induced a more rapid improvement to decrease symptoms and joint damage, a higher percentage of ACR responses, and lower erosion scores after 6 and 12 months. Tocilizumab monotherapy was also more effective than MTX monotherapy in improving more rapidly RA signs and symptoms. In the TEMPO trial, in which patients had previously failed the therapy with at least 1 DMARD other than metho-trexate, MTX combined with etanercept reduced disease activity, improved physical function, and slowed Rx progression more effectively compared to monotherapy with either agent up to 3 years. In the TEAR trial, conducted in patients previously treated with MTX with early-stage RA and poor prognostic factors, patients initially
treated with MTX monotherapy requiring a switch to combination with etanercept after 24 weeks showed DAS28 scores, ACR responses, and radiographic progression similar to those obtained in the group treated with the combination regimen since the start of the study, apparently reassuring about the possible damage of initial monotherapy. Conversely, the results of the HOPEFUL 1 trial in MTX-naïve subjects treated with adalimumab combined with MTX for 52 weeks or MTX with monotherapy for the first 26 weeks followed by 26 weeks of combined therapy, showed that patients who were in monotherapy for the first 26 weeks had worse radiographic progression compared to those treated with MTX plus adalimumab since the study start.

MTX in monotherapy versus tsDMARDs

In a study comparing MTX monotherapy with tsDMARD tofacitinib monotherapy and with their combination, MTX monotherapy was inferior to both tofacitinib monotherapy and combination therapy in terms of bone marrow oedema, synovitis, and erosive damage. A post-hoc analysis compared the efficacy of tofacitinib and MTX monotherapy in MTX-naïve patients with recent onset and long-standing RA. Response to tofacitinib 5 mg BID at 24 months was significantly greater in patients with early RA compared with established RA and superior compared with MTX, regardless of disease duration. Radiographic progression was significantly inhibited by tofacitinib compared with MTX in patients with early RA, while the difference did not reach statistical significance in established disease patients. A recent Cochrane meta-analysis compared the efficacy of MTX as monotherapy and in combination with other DMARDs, including tofacitinib, in patients with RA, either MTX-naïve or MTX-IR. MTX combined with tofacitinib was superior to MTX monotherapy, with a good safety profile.

Another trial compared MTX, baricitinib and their combination in patients with RA who received none or limited previous DMARD therapy. Results showed that baricitinib alone obtained a rate of ACR20 response that was similar to that of the combination therapy but significantly superior to that of MTX alone. Significant improvements of the combination therapy, compared to MTX alone, were observed also in terms of disease activity and physical function, as well as of radiographic progression.

Biologic DMARDs

The bDMARDs currently approved for RA include five TNFis (infliximab, adalimumab, etanercept, certolizumab...
Monotherapy in rheumatoid arthritis: a review / A. Doria & D. Zavaglia

... further four biological agents with different mechanisms of action: abatacept (co-stimulatory signal inhibitor), anakinra (IL-1 receptor antagonist), rituximab (monoclonal anti-CD20 antibody), and tocilizumab (IL-6 receptor blocker). Infliximab, rituximab, and golimumab are authorised only in combination with MTX, whereas tocilizumab, etanercept, certolizumab, and adalimumab are also approved for monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. We examine here bDMARDs for which data are available for RA monotherapy.

According to EULAR recommendations, bDMARDs should be considered only when the treatment target is not achieved by first-line csDMARD therapy, and in the presence of poor prognostic factors. Furthermore, it is recommended that bDMARDs are administered in combination with a csDMARD, usually MTX. Most of the clinical studies support indeed the superiority of the combination bDMARD/csDMARDs. However, as mentioned above, bDMARDs are used in monotherapy in about one-third of cases in the real-world setting and even with a higher rate when adherence to therapy is considered. A large trial showed that adherence to MTX decreases when patients with RA are prescribed a concomitant bDMARD (28), possibly because increasing the number of medications predisposes to a decrease of treatment compliance. Adherence is possibly a major cause of the high prevalence of bDMARD monotherapy in RA and bDMARDs are administered as first-line therapy more frequently than expected. Several trials have evaluated bDMARD use as first-line treatment, showing their significant superiority to MTX monotherapy (Table II). However, some controversial aspects emerged by reviewing the literature, with the consequent lack of consensus in favour of recommending bDMARDs as the first-line strategy among the EULAR Task Force experts. Relatively few clinical trials having as primary objective the efficacy of bDMARD monotherapy have been published. Further data come from observational studies, registry, or accessory results of clinical trials with different primary endpoints.

Very few studies evaluated infliximab in monotherapy. Data from a registry showed that infliximab administered in monotherapy in patients with contraindications to MTX showed similar efficacy to etanercept. In a retrospective study on 10,000 patients from the US Medicare database treated with a TNFis in monotherapy, the patients on infliximab were likely to discontinue the drug almost twice as much compared to those receiving a combination treatment. Adalimumab is approved for monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. In the PREMIER trial, adalimumab monotherapy induced the remission in about half the patients compared to adalimumab combined with MTX but led to a lower radiographic progression than MTX monotherapy. In the recent MONARCH trial comparing adalimumab with the new IL-6-inhibitor sarilumab, adalimumab monotherapy was less effective than sarilumab monotherapy in improving signs, and symptoms of the disease as well as physical function, with a similar tolerability profile.

In the RADIUS 2, including more than 4,000 patients, etanercept 3-year monotherapy obtained similar remission rate, as measured by Clinical Disease Activity Index (CDAI), to the etanercept/MTX combined therapy (about 35%), while in the TEMPO trial (682 patients) the rate of remission was higher with the combination (54%) than with etanercept monotherapy (39%). In the ADORE trial, an open-label study conducted in patients with inadequate response to MTX alone, the addition of etanercept to MTX was not clinically superior to etanercept monotherapy. In the 2-year COMET trial in patients with early RA, the removal of MTX from the combination with etanercept induced worsening of both clinical and radiological aspects compared with continued combination therapy. Similarly, in the COMETA trial, MTX-inadequate responder patients, who withdrew MTX after combination therapy with etanercept, had a worse outcome compared with patients maintaining combination therapy, especially those who had not reached remission or low disease activity during the first combination phase. The JESMR study also showed a statistically significant superiority of the combination of etanercept and MTX versus etanercept monotherapy, in both clinical and radiographic outcomes. Certolizumab pegol in monotherapy showed to be more effective than placebo in the FAST4WARD trial; in the subsequent REALISTIC trial, the ACR20 response was similar with certolizumab given as monotherapy and combined with csDMARDs.

In the GO-BEFORE trial, golimumab plus MTX was superior to golimumab and MTX alone, and there was no difference between the two agents administered as monotherapy. Likewise, in the GO-FORWARD study, the combination was more effective than golimumab and MTX alone. Rituximab was also more effective in combination with MTX than in monotherapy, but rituximab monotherapy was significantly superior to MTX monotherapy. Tocilizumab in monotherapy led to a dose-dependent reduction of disease activity compared to placebo and was superior to csDMARDs in improving signs and symptoms and reducing radiographic changes. In the ACT-RAY trial, the combination therapy of tocilizumab with MTX (add-on strategy) showed statistically significant differences in favour of the add-on strategy relative to some results (the percentage of patients with DAS28 remission, the change in patient’s global assessment of pain, the change in erosion score and the percentage of patients with no progression in Genant-modified Sharp score (GSS)). Tocilizumab monotherapy was also superior to adalimumab monotherapy in the ADACTA trial. The multicentre, non-interventional, prospective ACT-SOLO study analysed the real-life factors that influence tocilizumab use as monotherapy. The study first confirmed that tocilizumab was used as monotherapy in a high proportion of patients with RA in everyday clinical practice, then showed similar results between monotherapy and combination therapy at one year.
Janus-kinase inhibitors
Following the demonstration of the role of the large family of Janus kinases (JAK) in the autoimmune inflammatory response inhibitors of these kinases have been developed for the treatment of RA. Beyond the already existing JAK inhibitors tofacitinib and baricitinib, further JAK inhibitors are being developed for the management of RA, with different in vitro specificities for the different kinases of the JAK family. Tofacitinib, which primarily targets JAK1 and JAK3 and to a lesser extent JAK2, and baricitinib that selectively blocks JAK1 and JAK2 have been approved for RA treatment with the indication of patients failing to respond to at least one csDMARD. Tofacitinib and baricitinib belong to the class of the so-called targeted synthetic DMARDs (tsDMARDs) and, in according to the latest EULAR recommendations, should be considered, like bDMARDs, in addition to csDMARD in case of failure of the first-line therapeutic strategy. Though the EULAR Task Force recommended that tsDMARDs should primarily be combined with MTX, both tofacitinib and baricitinib were shown to be also effective in monotherapy (Table III). The EULAR Task Force also acknowledged that also patients with poor prognostic predictors had been included in most trials of tsDMARDs. Tofacitinib is the most extensively studied JAK-inhibitor so far and its effects on clinical and laboratory measures of RA are well documented in clinical studies, reviews, and meta-analyses. The ORAL Solo double-blind placebo-controlled phase III RCT demonstrated the efficacy of tofacitinib monotherapy in reducing RA signs and symptoms and improving physical function in pa-
Patients with inadequate response to disease-modifying drugs. In a further RCT with an active comparator, tofacitinib monotherapy was superior to adalimumab monotherapy in terms of ACR and DAS28 response rates. Pooled data from Mexican patients from four phase III studies and one open-label long-term extension (LTE) study included in the tofacitinib global RA program showed that tofacitinib monotherapy was effective up to 36 months in LTE studies. An open-label LTE study was conducted in Japanese RA patients treated with tofacitinib in monotherapy or in combination with MTX. Treatment duration was up to 5.5 years, with a median duration of 3.2 years. Tofacitinib showed a sustained efficacy profile, overall consistent with the profile observed in phase II and III studies and other LTE studies, pooled in the LTE study analysis. A systematic review and meta-analysis compared tofacitinib as monotherapy and in combination with MTX with bDMARDs and tsDMARDs (i.e. abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, tocilizumab, baricitinib) in the second-line treatment of moderate-to-severe RA. Forty-five RCTs were considered, overall showing that tofacitinib had similar efficacy to bDMARDs, both in monotherapy and in combination, in terms of ACR response, including ACR70.

**Table III. Summary of results of small molecules in monotherapy or in combination in patients with rheumatoid arthritis.**

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Study description</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleischmann</td>
<td>TFC in monotherapy vs. placebo</td>
<td>TFC monotherapy significantly effective on signs, symptoms and physical function</td>
</tr>
<tr>
<td>Fleischmann</td>
<td>TFC monotherapy vs. ADA monotherapy</td>
<td>TFC superior to ADA in terms of ACR and DAS28 response rates</td>
</tr>
<tr>
<td>Burgos-Vargas</td>
<td>Pooled data of 5 studies: TFC monotherapy vs. placebo</td>
<td>TFC significantly effective up to 12 months</td>
</tr>
<tr>
<td>Yamanaka</td>
<td>Open-label long-term extension study with TFC with or without background MTX</td>
<td>TFC safe and effective up to 5 years</td>
</tr>
<tr>
<td>Wollenhaupt</td>
<td>Pooled analysis of 2 long-term open-label studies with TFC in monotherapy</td>
<td>TFC safe and effective up to 4 years</td>
</tr>
<tr>
<td>Bergrath</td>
<td>Meta-analysis of TFC alone or combined with MTX vs. bDMARDs</td>
<td>TFC similar to bDMARDs, both in monotherapy and in combination, in terms of ACR response, including ACR70</td>
</tr>
<tr>
<td>Singh</td>
<td>Meta-analysis of TFC vs. bDMARDs all in monotherapy in csDMARD-IR</td>
<td>TFC similar to TNFis on SCR50, QoL, and remission rates</td>
</tr>
<tr>
<td>Fleischmann</td>
<td>TFC monotherapy vs. TFC and MTX combination therapy vs. ADA and MTX combination therapy in RA patients</td>
<td>TFC + MTX non-inferior to ADA + MTX. TFC monotherapy non-inferior to either combination therapy (inconclusive results)</td>
</tr>
<tr>
<td>Reed</td>
<td>TFC or TNFi monotherapy vs. TFC or TNFi combination therapy</td>
<td>No evidence that TFC monotherapy is less effective than TFC combination therapy</td>
</tr>
<tr>
<td>Keystone Genovese</td>
<td>BRC monotherapy in MTX-IRs</td>
<td>Effective on clinical measures and PROs</td>
</tr>
<tr>
<td>Dougados Emery</td>
<td>BRC vs. placebo both with background MTX</td>
<td>BRC significantly improved disease activity, remission rates, and physical function</td>
</tr>
<tr>
<td>Tanaka</td>
<td>BRC vs. MTX vs. combination of both</td>
<td>BRC superior to MTX; BAR + MTX superior to BAR alone</td>
</tr>
<tr>
<td>Taylor</td>
<td>BRC vs. ADA both in monotherapy</td>
<td>BRC superior to ADA on ACR responses and Rx progression at 12 and 24 weeks</td>
</tr>
<tr>
<td>Emery</td>
<td>BRC in monotherapy in MTX-IRs</td>
<td>BRC significantly effective on PROs</td>
</tr>
</tbody>
</table>

TFC: tofacitinib; ADA: adalimumab; MTX: methotrexate; BRC: baricitinib. IRs: inadequate responders; PROs: patient-reported outcomes.
had a previous inadequate response to MTX. The ORAL Strategy compares a Jak-inhibitor given as monotherapy or with MTX in an MTX-IR population. The results demonstrated non-inferiority (ACR50 response rates at month 6) for tocafitinib 5mg b.i.d. and MTX versus adalimumab and MTX. The results for tocafitinib monotherapy were defined statistically inconclusive because non-inferiority of tocafitinib 5mg b.i.d. (ACR50 response rates at month 6) to either adalimumab and MTX or tocafitinib and MTX was not shown. This study provides evidence that adding tocafitinib represents a treatment option in case of inadequate response to MTX. Regarding tsDMARDs real-world data novel tocafitinib data come from the CORRONA Registry. TNFis monotherapy is common in U.S. clinical practice although TNFis monotherapy is less effective than combination therapy, especially in biologic naïve patients or with one prior biologic agent treatment. From the CORRONA Registry, no evidence resulted that tocafitinib monotherapy was less effective than tocafitinib combination therapy or TNFi combination therapy, according to the outcome measures reported.

Baricitinib, another orally administered JAK-inhibitor, was shown to be effective and rather well tolerated in patients with RA with inadequate response to MTX and/or other csDMARDs or b-DMARD. MTX monotherapy, baricitinib monotherapy, and their combination were compared in patients with RA with no prior treatment with csDMARDs (no or limited exposure to MTX) or bDMARDs. The results showed that baricitinib alone obtained an ACR20 rate at week 12 significantly superior to that of MTX alone and similar results were obtained for combination therapy. Significant improvements, compared to MTX alone, were observed also in terms of disease activity and physical function. Moreover, radiographic progression was significantly reduced only for combination therapy.

Conclusions
According to the current recommendations, MTX and/or other csDMARD should be used as first-line treatment in patients with RA and a combination of csDMARDs with bDMARDs or tsDMARDs should be used in case of failure of the first-line therapy. However, it has been well documented that, bDMARDs are used as monotherapy in a consistent proportion of patients in the real world rheumatology practice. This likely suggests that there is a need for a monotherapy approach in RA with possible different reasons. Intolerance to MTX may be implicated, giving the potential low tolerability and the toxicities of this drug. Moreover, it has been shown that adherence to MTX therapy is often poor. Adherence to the prescribed treatment is particularly crucial in RA because the chronic course of the disease requires a long-term therapy and it has been demonstrated that poor adherence can negatively affect clinical outcomes. Furthermore, monotherapy may be a particularly valuable option for elderly patients, who often are affected by several comorbidities and have a reduced clearance. The review of the literature on DMARD monotherapy in RA highlighted the increasing evidence of the potential of some bDMARDs and tsDMARDs used as monotherapy, even if stronger evidence remains in favour of the combination of DMARD compared to monotherapies. Notably, tsDMARDs that can be administered orally, having a rapid onset of action and efficacy as monotherapy, may represent an important option for RA therapy. Specifically designed comparative trials will be required to show further evidence of the clinical value of future RA monotherapy approaches. However, it is worth to be recalled that a thoughtful consideration of patients’ preferences and expectations should also be adopted when selecting a therapy for RA.

Acknowledgments
Medical writing and editorial support were provided by CDM and TBWA and were funded by Pfizer.

References
14. HEIBERG MS, KOLDINGSNES W, MIKKEL-
Monotherapy in rheumatoid arthritis: a review / A. Doria & D. Zavaglia

Clinical and Experimental Rheumatology 2019


LISTING J, STRANGFELD A, RAU R et al.: Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low—results from RABBIT, the German biologic register. Arthritis Res Ther 2006; 8: R66.


GRIJALVA CG, CHUNG CP, ARBOGAIST PG, STEIN CM, MITCHEL EF, JR., GRIFFIN MR: Assessment of adherence to and persistence on disease-modifying anti-rheumatic drugs (DMARDs) in patients with rheumatoid arthritis. Med Care 2007; 45 (Suppl. 2): S66-76.


and combination therapy in the treatment of rheumatoid arthritis: results from the RA-
52. EMERY P, BREEDVELD FC, HALL S et al.: Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to se-
vere rheumatoid arthritis (COMET): a ran-
domised, double-blind, parallel treatment
53. BATHON JM, MARTIN RW, FLEISCHMANN RM et al.: A comparison of etanercept and methotrexate in patients with early rheuma-
54. VAN DER HEIDE D, KLASREKOS L, LAN-
DEWE R et al.: Disease remission and sus-
tained halting of radiographic progression with combination etanercept and metho-
55. VAN DER HEIDE D, KLASREKOS L, RODRI-
GUEZ-VALERDE V et al.: Comparison of etanercept and methotrexate, alone and com-
bined, in the treatment of rheumatoid arthri-
56. MORELAND LW, O’DELL JR, PAULUS HE et al.: A randomized comparative effectiveness study of oral triple therapy versus etaner-
57. O’DELL JR, CURTIS JR, MIKULS TR et al.: Validation of the methotrexate-first strategy in patients with early, poor-prognosis rheu-
matoid arthritis: results from a two-year ran-
58. YAMANAKA H, ISHIGURO N, TAKEUCHI T et al.: Recovery of clinical but not radiographic outcomes by the delayed addition of adali-
numab to methotrexate-treated Japanese patients with rheumatoid arthritis: 52-
week results of the HOPEFUL-1 trial. Rheu-
59. CONAGHAN PG, OSTERAARDA M, BOWES MA et al.: Comparing the effects of tofaci-
60. FLEISCHMANN RM, HUIZINGA TW, KAN-
AUGH AF et al.: Efficacy of tofacitinib mon-
otherapy in methotrexate-naive patients with early or established rheumatoid arthritis. RMD Open 2016; 2: e000262.
61. FURST DE, KEYSTONE EC, BRAUN L et al.: Updated consensus statement on biological agents for the treatment of rheumatic disease-
62. VICENTE RABANEDA EF, HERRERO-BAEU-
63. NASHI P, NAYLAGER S, GENOVESE MC et al.: Immunosuppression, safety, and efficacy of abatacept administered subcutaneously with or without background methotrexate in pa-
tients with rheumatoid arthritis: results from a phase III, international, multicenter, paral-
64. BRENSHAIN B: Anakinra as a new therapeu-
tic option in rheumatoid arthritis: clinical results and perspectives. Clin Exp Rheuma-
65. FECHTENBAUM M, MD YUSOF MY, EMERY P: Certolizumab pegol in rheumatoid arthri-
66. CURTIS JR, YANG S, CHEN L et al.: Predict-
ing low disease activity and remission with early treatment response to antitumour ne-
crosis factor therapy in patients with rheu-
67. CANNON GW, WANG BC, PARK GS, KOENIG A, COLLIER DH, KEYSTONE EC: Remission in rheumatoid arthritis patients treated with etanercept monotherapy: clinical practice and clinical trial experience. Clin Exp Rheu-
matol 2013; 31: 919-25.
68. GENOVESE MC, HAN C, KEYSTONE EC et al.: Effect of golimumab on patient-report-
ed outcomes in rheumatoid arthritis: results from the GO-FORWARD study. J Rheuma-
69. NAM JL, RAMIRO S, GAUJOUX-VIALA C et al.: Efficacy of biological disease-modifying antirheumatic drugs: a systematic lit-
erature review informing the 2013 update of the EULAR recommendations for the man-
70. RICHTER A, STRANDGELF A, HERZER P et al.: Sustainability of rituximab therapy in different treatment strategies: results of a 3-year follow-up of a German biologics reg-
71. GABAY C, EMERY P, VAN VOLLENHOVEN R et al.: Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a ran-
72. NAKASHIMA Y, KONDO M, MIYAHARA H, IWAMOTO Y: Drug delivery options to in-
crease patient adherence and satisfaction in patients with rheumatoid arthritis despite methotrexate therapy: results through 2 years of the GO-
73. EDWARDS JC, SZCZEPANSKI L, SZECHINSKI P et al.: Efficacy of B-cell-targeted therapy in rheumatoid arthritis despite methotrexate therapy: results through 2 years of the GO-
74. KEYSTONE EC, GENOVESE MC, HALL S et al.: Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: results for 2 years of the GO-
75. EDWARDS JC, SZCZEPANSKI L, SZECHINSKI P et al.: Efficacy of B-cell-targeted therapy in rheumatoid arthritis despite methotrexate therapy: results for 2 years of the GO-


