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Rational Usage of Disease Modifying Anti-Rheumatic Drugs with the Guidance of EULAR and ACR Suggestions

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Abstract

Disease modifying anti-rheumatic agents are the cornerstone in management of Rheumatoid Arthritis and when used correctly they are life-saving. As the number of the agents increases, detailed guidelines become more and more important for clinicians to set safe and effective regimens. Herein, we combined the EULAR and ACR recommendations for clinicians and also pointed some important facts peculiar to our country.

Keywords

DMARD, Rational, EULAR, ACR

1. Introduction

The disease modifying anti-rheumatic drugs (DMARDs) are the cornerstone in management of Rheumatoid

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Arthritis (RA). These agents are effective in suppression of inflammation, relieving the symptoms, maintaining remission and inhibiting radiologic damage. Recently, a new nomenclature was published for DMARDs by European League Against Rheumatism (EULAR) and these agents were classified as synthetic and biologic DMARDs. Synthetic DMARDs include Methotrexate (Mtx), Sulfasalazine and Leflunomide as conventional synthetic DMARDs and Tofacitinib as targeted synthetic DMARD. On the other hand, tumor necrosis factor alpha inhibitors: Infliximab, Etanercept, Adalimumab, Golimumab and Certalizumab as well as Abatacept, Rutiximab, Tocilizumab and Anakinra are named as biologic original DMARDs. Biosimilar Infliximab is the only DMARD in the biosimilar group [1]. As the number of the agents increases, the decision for the most optimal treatment regimen becomes a problem for some clinicians. In 2010, EULAR has published recommendations to guide clinicians and these recommendations were updated in 2013 [2] [3]. Unlike EULAR, American College of Rheumatology (ACR) does not divide DMARDs as synthetic or biologic and according to ACR, Minocyclin and Hydroxychloroquine are still accepted as DMARD. The ACR guidelines were published in 2008 and updated in 2012 [4] [5].

Herein, we will discuss the general recommendations from two groups and also try to define the vital points in deciding optimum DMARD therapy.

2. Overarching Principles

EULAR has determined 3 overarching principles.

1) *Best care and shared decision*; this principle is of great importance because the compliance of the patient to the therapy and also the mood may be improved by this strategy. The patient should know everything or at least the most important points about Rheumatoid Arthritis and the disabilities that the disease may cause. Furthermore, patients should know that RA is not incurable because this idea will lead to depression and hopelessness. On the other hand, learning about the efficacy and adverse effects of the DMARDs may increase the patient compliance to DMARD therapy and also may increase the treatment effectivity.

2) *Rheumatologists are the specialists*; Rheumatoid Arthritis is a systemic disease with multiple disease and treatment related complications. Ideally all the complaints of a RA patient should be evaluated by a Rheumatologist but the number of Rheumatologists in most countries and also in the world is not adequate therefore experienced physicians other than Rheumatologists and also nurses may decrease the workload of the specialists. Education programs for internists, family doctors and nurses should be arranged.

3) *High individual, societal and medical costs*; during the last two decades variable treatment options for RA has been discovered. From now on, only symptomatic relief in no more the target of the treatment and achieving remission or at least low disease activity is highly recommended. On the other hand, these new treatment options are very expensive and have frightening adverse effects as malignancy and tuberculosis. Therefore, Rheumatologist should be very careful while deciding the treatment regimen in terms of cost, adverse effects and also efficacy.

3. Recommendations

There are totally 14 recommendations and the aim of them is to treat any RA patient as early, effectively and safely as possible. These recommendations also guide the clinicians about biologic DMARD therapies.

1) *Early DMARD therapy*; disease modifying agents and especially Methotrexate are the mainstay of the therapy in RA. Symptomatic relief may be achieved by nonsteroidal anti-rheumatic drugs as well as by corticosteroids but the radiologic progression may not be prevented favorably, therefore earlier diagnosis and earlier DMARD therapies are essential. The American College of Rheumatology 2010 classification criteria for RA is useful in earlier diagnosis and also beginning of DMARD therapies before any radiologic damage occur [6].

2) *Target remission or at least low disease activity*; with the novel treatment options, patients have the chance to achieve remission defined as a score lower than 2.6 in disease activity score for 28 joints. If possible, patients achieving remission have better functional and structural outcomes. On the other hand, some patients with established disease cannot reach this target and low disease activity may also be an alternative goal. Symptomatic relief or partial disease control with moderate disease activity are not acceptable anymore. According to the literature, with novel agents, targeting remission is no more a Utopia [7]-[14].

3) *Monitoring and therapy adjustment*; monitoring intervals of any patient should depend on the disease activity, every month for very active disease and yearly monitoring for stabilized disease may be acceptable. On

the other hand, treatment modifications may be done after 3 months of therapy with maximal doses if no improvement have been achieved and clinicians should wait 6 months to reach treatment targets. Maximal efficacy of the biologic and conventional agents will be seen after 6 months [15]-[18].

4) *Methotrexate should take place in the first step if possible*; Mtx in combination or as monotherapy is highly active against RA and is the anchor drug in the therapy. Mtx, Mtx + glucocorticoids, Mtx + other DMARDs are all affective options and other than patients with low disease activity all should take Mtx. DMARD naïve patients and patients previously treated with other DMARDs will benefit from Mtx [18]-[25].

5) *If Mtx is contraindicated other cDMARDs may be preferred*; Renal and Hepatic diseases and Mtx related lung diseases may limit usage of Mtx and in this case, Sulfasalazine and Leflunomide are effective in monotherapies or in combination. Optimal dose for Sulfasalazine is 3 - 4 gr/day and for Leflunomide 20 mg/day. These two agents have similar efficacies with Mtx. Gold salts (especially injectable forms) are also as effective as Mtx but are unavailable in most countries and are less frequently used. Previously used agents as azathioprine, cyclophosphamide and cyclosporine are no longer recommended [26]-[33].

6) *For DMARD naïve patients conventional DMARDs* (*monotherapy or combinations*) *should be the first step with or without glucocorticoids*; although Mtx monotherapy is highly effective with low toxicity, Mtx including csDMARD combinations may be more effective than Mtx monotherapy therefore, csDMARD combinations should be also kept in mind for DMARD naïve patients. These combinations are also as effective as Mtx and bDMARD combinations which is no longer preferred or recommended in the first step [34]-[40].

7) *The duration and dose of corticosteroid therapy should be limited*; Corticosteroids are very effective agents against inflammation and add a lot to patients with RA but have various adverse effects. Therefore, EULAR recommends low dose; 7.5 mg/d prednisolone or equivalents for only 6 months. Their benefit/risk profile should be estimated carefully [41]-[45].

8) *If the first DMARD strategy fails change to another csDMARD strategy for patients without poor prognostic factors, or add a bDMARD if poor prognostic factors are present*; the presence of high disease activity, CCP or RF positivity or early joint damage are defined as poor prognostic factors for RA. EULAR recommends addition of another csDMARD for low risk patients or addition of bDMARD for high risk patients. Again Mtx in an effective dose should take place in these regimens [45]-[47].

9) *If all MTX and/or other csDMARD* (*+/−steroid*) *strategies fail, bDMARDs + Mtx* (*TNF inhibitors, abatacept, tocilizumab and rituximab*) *should be commenced*; when the csDMARD regimens fail to achieve treatment targets in the 6th month or at least improvement in 3rd month, than bDMARDs should be commenced with Mtx. All biologic agents other than anakinra have similar efficacy and safety profile therefore, anyone may be prescribed but the data and experience with anti-TNF agents are higher which make them more preferable. On the other hand, Rutiximab may be a safer option in Tbc endemic regions and also for patients with recent malignancies. Usage of bDMARDs for DMARD naïve patients was highly discouraged by EULAR because there are limited data for this treatment regimen and most patients respond to csDMARDs very well [24] [48]-[52].

10) *If one bDMARD fail than another one may be commenced, anti-TNF may be switched to another anti-TNF*; the efficacy of any biologic agent are known to be similar to each other therefore, when one fails than another one may be preferred and the failure of one anti-TNF do not mean that other will not work. In near future IL-6 blockers will be available and these agents may also be switched to each other but only biosimilar infliximab should not be switched with bio-original infliximab [53]-[55].

11) *Tofacitinib may be only considered when all bDMARDs fail*; as a JAK inhibitor Tofacitinib is not a biologic agent but a targeted cDMARD and statistical data for inhibition of radiological damage failed to show difference from placebo ($p = 0.06$). Serious infections as well as opportunistic infections are reported to be frequent with Tofacitinib. Furthermore, the experience and data are extremely limited and that is why EULAR recommends Tofacitinib after the failure of all biologic agents [56]-[59].

12) *After cessation corticosteroid in a patient with disease remission, bDMARDs may also be tapered*; for patients with low disease activity or remission after the cessation of corticosteroids, one can consider tapering the dose of the biologic agent. These experiences exist for anti-TNF agents mostly but novel data suggest that other biologics may also be tapered. The most important point is that the steroids should be tapered and stopped first and the remission or at least low disease activity is maintained during the tapering of biologic agents [60]-[63].

13) *After long term remission a careful dose reduction in csDMARDs may be discussed with the patient by the clinician*; total cessation of cDMARDs result in 70% relapses in patients with RA, therefore dose reduction but not cessation is recommended. The maintenance of remission is necessary while reducing the dose [64]-[66].

14) *Not only disease activity, but also progression of the structural damage, comorbidities and safety issues are all important for therapy adjustment*; achievement of remission or at least low disease activity is as important as reaching these goals with lowest and acceptable toxicities. Therefore, the comorbidities of the patients are directive in therapy adjustment. Furthermore, some patients with low disease activity still have radiologic progression of the structural damage and these patients also should be candidates for therapy adjustment although treatment goals have been achieved [67]-[71].

4. Tuberculous Screening

The American College of Rheumatology recommends screening all RA patients who are candidates for biologic DMARD therapy for latent tuberculosis if there is any risk factor. The recommended initial test is tuberculin skin test (TST) or interferon gamma release assay (IGRA). The false positive ratio of TST for patients with BCG vaccination is very high therefore IGRA may be more useful for this group. Any patients with positive test result should be screened with chest X-ray also and if active Tbc is suspected than sputum examination should also be done. Negative test results in screening without any risk factor or clinical suspicion do not need further evaluation but these screening tests also have high false negative results in immunosuppressive patient therefore clinical suspicion and risk factors may be assessed in detail. Repeated tests may be useful for these patients. For patients with positive test results at least 1 month of prophylaxis is necessary before biologic therapy and for patients with active tbc the tbc treatment should be completed before biologic DMARDs. According to recent articles, anakinra, rutiximab and abatacept do not increase the risk of Tbc activation but Tocilizumab may increase the risk according to the registries therefore, until adequate data are published all patients should be examined in detail for latent tuberculosis and near anti-TNF agents perhaps tocilizumab patients may take anti-Tbc prophylaxis. The experience with rutiximab from oncology patients is large and probably adequate to say that the activation of latent tuberculosis risk does not increase [5].

5. Vaccination

In routine clinical practice, vaccination is usually forgotten and overlooked. The routine vaccines are the killed (pneumococcal, influenza intramuscular, and hepatitis B), recombinant (human papillomavirus [HPV] vaccine for cervical cancer), and live attenuated (herpes zoster) vaccines and ACR recommends all type of vaccination before any DMARD therapy. For patients who are already taking a conventional or bDMARD, ACR recommends pneumococcal (killed), influenza intramuscular (killed), hepatitis B (killed), and HPV vaccine (recombinant) to be undertaken. On the other hand, herpes zoster vaccine for patients under any biologic DMARD should be avoided [5].

6. Special Conditions

In case hepatitis C only Etanercept may be recommended but for patients with untreated chronic hepatitis B or for hepatitis B patients with Child B or C cirrhosis the biologic agents should be avoided. For patients with treated solid malignancy > 5 years ago or treated non-melanoma skin cancer > 5 years ago all biologic agents may be preferred but for the first 5 years period Rutiximab may be suitable. Similarly all patients with treated melanoma skin cancer or lymphoproliferative diseases are good candidates for Rutiximab. On the other hand, for patients with NYHA class III/IV hearth failure and with an ejection fraction of lower than 50% all biologic agents should be avoided [5].

7. Important Points Peculiar to Our Country

The number of the Rheumatologist in our country is not adequate to serve all the RA patients in ideal manner. Therefore, the internal medicine and physical medicine specialist should be educated well for management of RA patients. Early diagnosis and effective therapy usually fails for rheumatology patients which means that all the practitioners should be aware of rheumatologic diseases and should consult any patients as early as possible to any rheumatology specialists. One of the main problems in our country is the unrestrained corticosteroid usage. Both the patients and the clinicians are not aware of the long term adverse effects.

Tuberculous screening is another problem in our country because all the population has received BCG vaccination which means that clinicians will face high false positive results with TST. IGRA is not widely available

and is not refunded by the government therefore unnecessarily high Tbc prophylaxis and additional tests are done. Tbc is endemic in our country and this means that clinicians should be extra careful about latent Tbc activation.

8. Discussion

By time the therapeutic options and treatment targets change and the treatment guidelines are updated. Targeting remission or low disease activity, if possible, is the matter of the last 2 decades. Lower doses of corticosteroids with shorter duration, beginning the therapy with cDMARDs but not with bDMARDs and using bDMARDs in combination with Mtx are the other novel recommendations.

Stating that there are no differences between any biologic agent, original or biosimilar, in case of safety and efficacy, frequent controls for active disease, waiting 6 months for maximal efficacy if improvements have been achieved in the first 3 months are also very important points. One of the most important recommendations is that, Mtx should be the first DMARD to be preferred for any RA patients if there are no contraindications.

The recommendations about Tofacitinip were also new and directive for clinicians. Furthermore, Tbc screening and vaccination were also summarized by ACR for an ideal management. The importance of poor prognostic factors for disease modification, tapering and stopping corticosteroids, tapering the dose of biologic agents and the role of structural damage for treatment adjustment was defined.

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