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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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UPDATE ON THE USE OF METHOTREXATE IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS

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Abstract.

Rheumatoid arthritis (RA) is an auto-immune disorder described by permanent inflammation of the articular synovial membrane. Non-treated RA can cause gradual joint damage, ending in complaint, poor lifestyle, and an upright ratio of death. Approximately one percent of the people are involved, and the disorder begins, in general, appears during the third and fifth decades of age, with more occurrences in females. The treatment is complicated as well as involves various stages of medications with variable methods of application as well as non-pharmacologic methods. The extra prevalent are disease person's culture, then, sports and mechanical and behavioral therapy. Due to more chance of ischemic heart disease, trials should be increased to lessen the assisting behaviors such as cigarette smoking, high lipid profile, elevation of blood pressure, and high body mass index.

Key words. Rheumatoid arthritis, methotrexate, disease modifying anti-rheumatic drugs, glucocorticoids.

Introduction.

The first goal in treatment of rheumatoid arthritis (RA) is to cure pain and oedema rapidly as well as to relieve the inflammation, glucocorticoids (GC) are implicated largely in recent disease attacks either by mouth or in intra-articular ways. GC is given by mouth for a brief period (up to three months) merely in low doses to block unwanted events as possible (Figure 1). The management of inflammatory processes over a prolonged time requires the introduction of traditional Disease Modifying Anti-Rheumatic Drugs (DMARDs) to decrease the need for glucocorticoid use. Today, multiple chances may be considered as dares or oppositions [1,2].

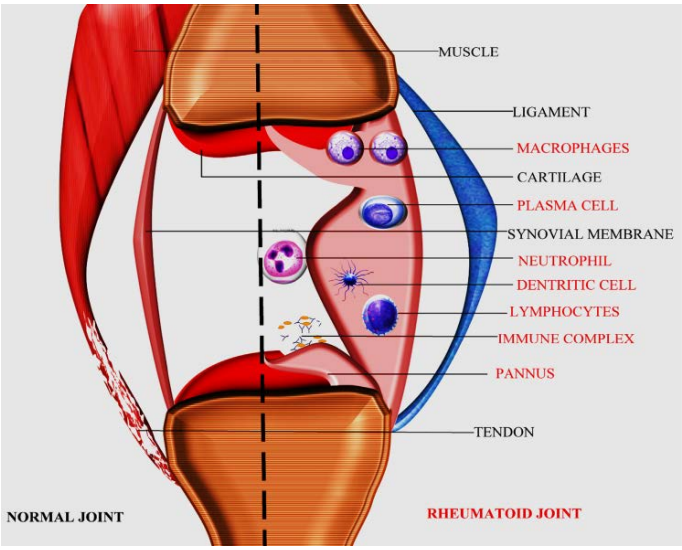

Figure 1. *Rheumatoid pathology[2].*

During the 1980s, as well as to recent medications to manage rheumatoid arthritis, recent standards were discovered to measure the results of therapeutic use. furthermore, it was noticed that the recent DMARDs were almost little applicable for more than 2 years, structural breakdown usually appeared clear on the picture of radiographs during the early 2 years after the beginning of the disease and a small dose every week by the mouth of methotrexate (MTX), a medication usually prescribed to manage psoriasis, not merely good in treating polyarticular psoriatic arthritis (PsA) but as well as was non-harmful and highly accepted when used in those with rheumatoid arthritis. Using both, these findings led to the US Food and Drug Administration (FDA) agreement of MTX for the management of rheumatoid arthritis in 1988 and to a new way of the conventional sequential approach to the pharmacological treatment of rheumatoid arthritis [3] (Figure 2).

Methotrexate.

By the 1990s, MTX was considered the main step of treatment of most rheumatologists to manage patients with rheumatoid arthritis in the USA, although rapid effective trials concluded that, at least during the first year of treatment, other items, including sulfasalazine (SSZ), were with the same efficacy. Attempts were encouraged to define approaches involving increasing the tolerance to more of the MTX dosage system (such as by subcutaneous route), thereby elevating its affectivity, and patients with rheumatoid arthritis were mostly capable of complying MTX for prolonged durations of time, which was not often the state with recent DMARDs. Although this, some patients were not able to comply with the dosage needed to perform higher results or still MTX non-well responders [3].

In addition, it was not recommended for others, like a young female approaching gestation or those who drink alcoholic beverages as usual. In addition, MTX monotherapy cannot ideally lead to disease control; continuous MTX management was needed to keep a therapeutic response and a lot of those who had permanent disease progression even during using this medication. A few recent studies encouraged the ability that treatment with both DMARDs ± CSs might be more beneficial than MTX monotherapy, and this is a way of thinking that progresses around 20 years after that. Although monotherapy of MTX is more effective in most recently diagnosed- rheumatoid arthritis patients, depending on the health insurance model (cost-effective or not), the National Institute for Health and Clinical Excellence (NICE) in the UK advises that together use of DMARDs plus short period of steroids as first-line treatment as soon as possible after starting of disease, while typically during three months of beginning of continuous features of rheumatoid arthritis in well-matched patients who do not include prevention from this method [3].

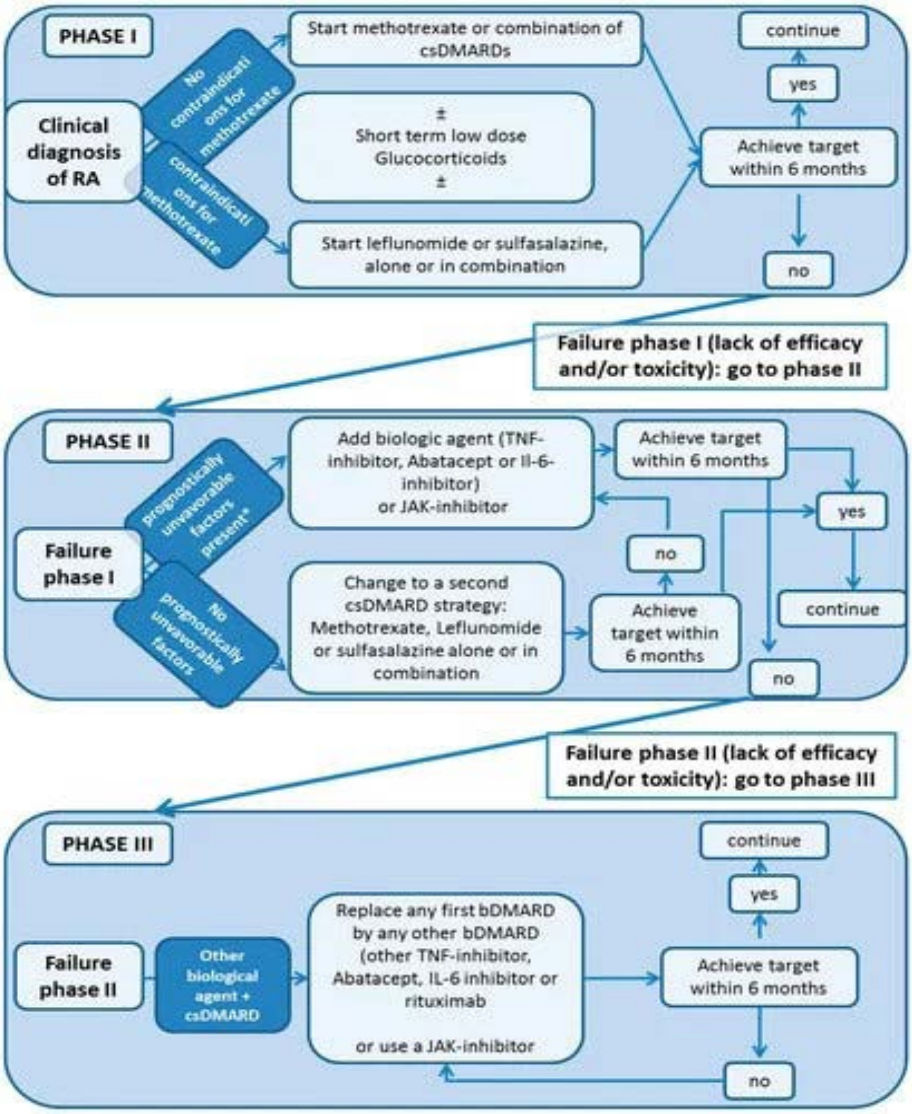

Figure 2. *Algorithm adapted for management of RA recommendations [3].*

Strategy for management of AR.

More early, in the 2012 update of publishing done priority regimens, the ACR, as well as an aim of lowering disease progression or control, advises one DMARD treatment as a single agent (drug not determined) in those with a disorder period of less than half of year with decreased disorder progression (activity defined by accepted Disease Activity Score (DAS) levels) and to medium or increased disease activity no bad prognosis (occurrence of one or more of useful restriction, extra-articular damage, active RF or ACPAs, and bone defects). Combining DMARDs (either two or more DMARDs, a lot of which are MTX dependent) was advised to remain patients with recent disorders, a decrease of depending on that method in patients before the starting of biologic responding drugs [3].

Diagnosis of AR.

The European League Against Rheumatism (EULAR) showed Disease Activity Score (DAS-28) involves the estimation of the count of diseased small joints, measurement of active inflammation indicators, and patient national good state score. Rheumatoid arthritis is recognized by levels of Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPAs). Positively serum results for Rheumatoid Factor may occur in about sixty to eighty percent of previously diagnosed rheumatoid arthritis patients, while less time occurs in recent rheumatoid arthritis (less than fifty percent). Anti-Citrullinated Protein Antibodies have a sensitivity of 62–72% and a specificity of 94–97% earlier for rheumatoid arthritis. It can be diagnosed earlier in rheumatoid arthritis, usually occurring preceding Rheumatoid Factor, and noticed preceding symptoms of the disorder. When Anti-Citrullinated Protein Antibodies-negative patients occur, another autoantibody usually measured, involving, anti-malondialdehyde acetaldehyde, anti-carbamylated proteins, 14-3-Beta, anti BRAF, anti-Sa, anti-CarP and anti PAD3/PAD4 antibodies (Figure 3) [3,4].

Non-steroidal anti-inflammatory Drugs (NSAIDs); like naproxen, ibuprofen, ketoprofen, diclofenac, piroxicam, and celecoxib, are increasingly implicated as symptom-relieving drugs. Disease-modifying anti-rheumatic Drugs are different drug groups which considered a cornerstone of management for rheumatoid arthritis [5].

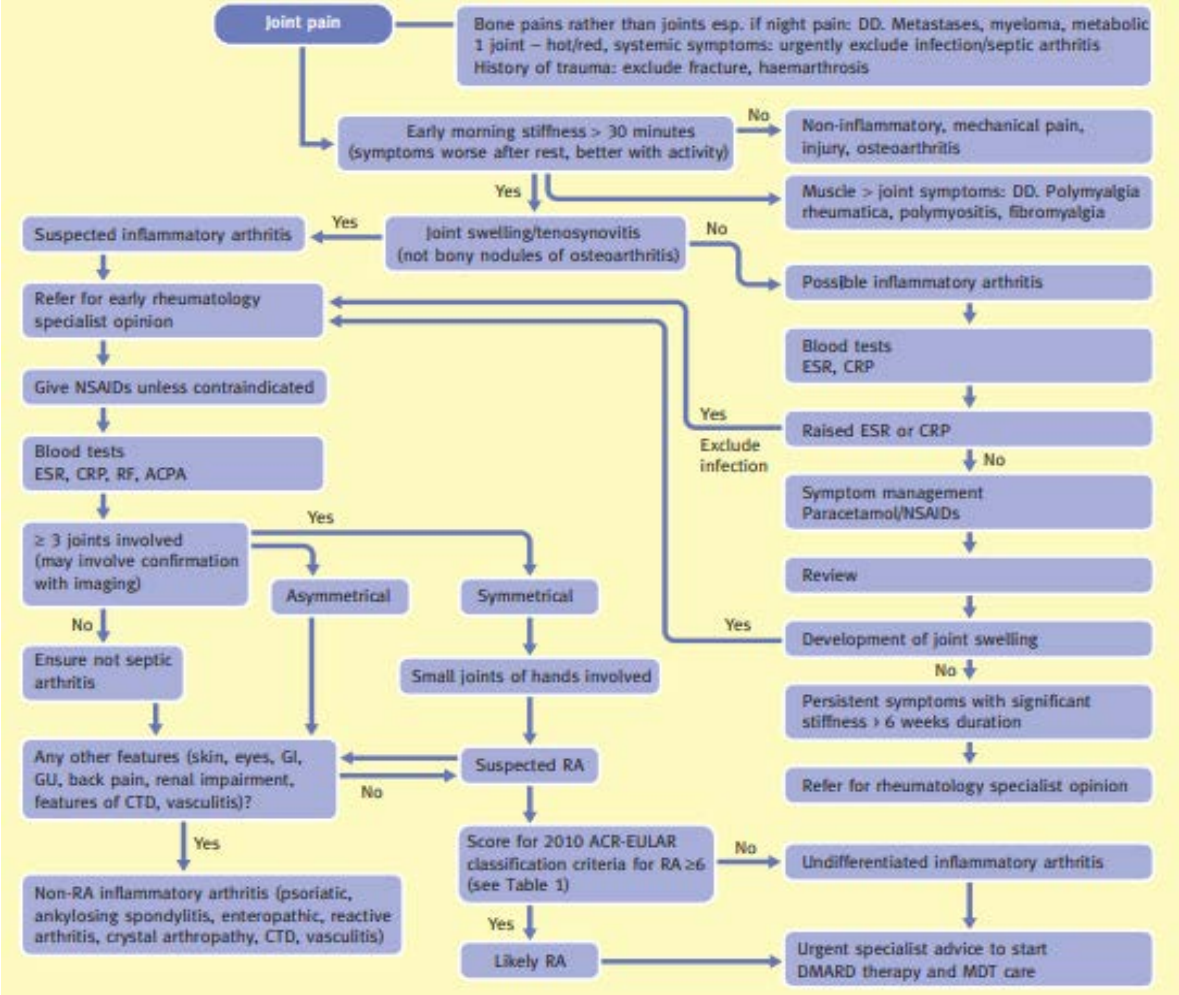

Figure 3. *Diagram for stepwise diagnosis of RA [4].*

DMARDs are categorized as traditional manufactured DMARDs (csDMARDs, that involve MTX, hydroxychloroquine (HCQ), sulfasalazine (SSZ) and leflunomide), targeted synthetic DMARDs (tsDMARDs, that involve baricitinib and tofacitinib), and biological DMARDs (bDMARDs, such as abatacept, Adalimumab, secukinumab, anakinra and tocilizumab). MTX is considered the initial drug line of traditional DMARDs. Sulfasalazine or leflunomide is implicated in state when the MTX is not recommended. In patients showing poor response to therapy, or a bad prognostic state, combination with a bDMARD or tsDMARD is advised. The corticosteroid drugs, despite being active in decreasing symptoms like pain and development of the disorder, are indicated for a short period as an adjuvant therapy due to their side effects [6,7].

MTX (four-amino-ten-methylfolic acid), an anti-folate drug which has been accepted for the management of rheumatoid arthritis patients in the 1980s, is a pro-drug that acting while active when glutamate within cells, showing increase connectivity for di-hydro-folate reductase (DHFR) [8]. The by-mouth formula of MTX is withdrawn mainly from the small intestine through an active transfer pathway demanding the folate carrier. Regarding bioavailability, MTX reach ranges from 30 per cent to 70 per cent as well as becomes steady after a single by-mouth dose >15 mg, indicating a withdrawing limit. Intracellular MTX is gradually polyglutamated (MTXGlun) [10].

Actions of methotrexate.

The glutamate and deglutamation are usually done competitively, fixed status of concentrations of MTX inside the cells are reached approximately in time of 7 months with inter-individual variations because of variable polyglutamation ratios. The main key indicators of MTXGlun levels are kidney performance, age as well as MTX dosage. The serum level of MTX lowers quickly after an intravenous injection. The half-life time of the drug is approximately 4.5 hours to 10 hours but within cells, MTX stayed longer time after its serum clearance. The glomerular filtration is the main renal route for excretion of MTX and active tubular excretion. The MTX is delivered nonchanged through the kidney in about seventy-five per cent with major inter-individual variation [11].

The oral MTX absorption is restricted by an active transport mechanism leading to a decrease in the bioavailability of upper doses of MTX. Incidentally, there are two ways to increase bioavailability either by dividing the dose given by mouth or changing to another way as parenteral. The low onset of the acting of MTX is attributed progressively to polyglutamation and the delay before maximal advantage [12].

The rate of glutamation is different between patients, certain patients have minimum glutamation ratios and a fairly minimum dosage plan, which will increase the duration needed for a satisfactory drug level to be accomplished. This perhaps be harmful, as increased intracellular MTXGlun concentrations have been related to good clinical response. When compared with by mouth route, the subcutaneous injection method was accompanied by an essential elevation in MTXGlun concentrations. Renal function influences the generation of MTXGlun. Because of the aggregation of polyglutamated particles in tissues, the effect of MTX as an anti-inflammatory in rheumatoid arthritis patients is longer despite its short plasma half-life time. Subsequently, the MTX is mainly excreted by the kidney, some conditions like renal impairment, or competing elimination of different drugs in patients receiving polypharmacy will increase its serum half-life time [12].

The last update guidelines, the management of RA should be onset directly with MTX, the first DMARDs used alone. These attitudes were suggested to obtain good patient outcomes with susceptibility to better feedback of the drug. During management of the rheumatoid arthritis, a MTX regimen is usually given once weekly oral single dose, or in split weekly dosages manner [13].

The mechanism of action of MTX when given as a large dose in the treatment of malignant diseases depends on antagonising folic acid causing a blockage of synthesis of pyrimidines and purines and hence block of DNA multiplication and cellular growth. This mechanism also was attributed to MTX action in multiple progressive autoimmune diseases, such as rheumatoid arthritis [14]. Maximum activity is obtained when it introduces the cell, MTX is required to metabolize to poly-glutamate formula (MTXPG). This was usually done by the enzyme folypolyglutamate synthetase, and the action of GGH antagonized this reaction. MTXPGs block di-hydro-folate reductase, thymidylate synthetase and AICAR Transformaylase (encoded by ATI Cyclohydroxylase gene). Blockage of DiHydroFolate Reductase (DHFR) and Thymidylate Synthase (TYMS) will lead to a serial block of biosynthesis of purine and pyrimidine, impairing of multiplication of DNA and cellular growth [15].

Inhibition of the 5-Amino-Imidazole-Carboxamido-Ribonucleotide (AICAR) transformylase will result in higher AICAR concentrations that lead to aggregation and liberate of Adenosine is one commonly accepted mechanism. Finally, multiple Adenosine receptors would be activated to generate the Anti-Inflammatory effects of MTX [16].

A discovery recorded that MTX could block the effect of T cells and the action of fibroblast-like synoviocytes. The other current thesis is blocking DiHydroFolate Reductase (DHFR) to lower tetrahydrofolate cofactors and deplete cells, MTX and its polyglutamate formula first inhibit firstly new biosynthesis of nucleotide. Subsequently, multiple enzymes such as DiHydroFolate Reductase and thymidylate synthase included in steps of the generation of purines had impaired because of the aggregation of dihydrofolates and MTX polyglutamate (MTXGlu), these mechanisms mentioned above associated with blockage of NF-κB action and could suggest how MTX is superior in the management of RA [17].

Depending on the European League Against Rheumatism (EULAR) guidelines, the first step in the management of rheumatoid arthritis with traditional synthetic DMARDs, perfectly MTX with small doses of steroids. The dosage use of MTX shown to be lower in comparison with other conventional synthetic DMARDs as MTX improves the synergistic effects of biological DMARDs. These results showed the cause for the unique state of MTX and considered the initial line of DMARDs in the treatment of rheumatoid arthritis. However, the stoppage of MTX within the therapy was chiefly because of toxic effects in place of ineffectively [18,19].

The most designed pathway for treatment-naïve, recent rheumatoid arthritis (RA) patients is commonly Treat-to-target (T2T). A T2T method can cause perfect and drug-free disease control, while usability to reach disease control resulting in early destruction in the disease process. So, each should importantly an effort to obtain large remission ratios as soon as possible, using the good clinical plans already known. A combination of MTX and steroid class is the first main step in the T2T system. Anyway, MTX like usually applied imperfectly in rheumatoid arthritis patients for a lot of causes, involving low compliance, bad tolerability, and safety aspects. New evidence has recommended that new planned manufactured DMARDs (t,s-DMARDs) like the (Janus-kinase) blockers with conjugation of steroids obtained good results of recent rheumatoid arthritis other than traditional management. A method may have good aspects in terms of patients' final results, although some worry about dangerous unwanted effects should need to be recorded [20].

A non-complicated drug depended on an individual collection plan, Herein, had suggested for decorating enzymatic-bounded protein nanoparticles. MTX with its hydrophobia might stimulate individual- accumulation of (form HSA-SOD-MTX Nano-medicine) human serum albumin (HSA) and superoxide dismutase (SOD). At the end of parenteral administration, the double-model filming technique involving fluorescent filming or (SPECT) (single-photon emission computed tomography) /CT filming shows an extra collection of HSA-SOD-MTX nanoparticles (cyanine 5.5 (Cy5.5) or 125I) in the articular surfaces of protein (collagen-stimulated arthritis) (CIA) in rats. Noticeably, applying of combined treatment for enzyme (SOD) to remove the reacting O2 particles in addition to MTX for inhibition of inflammation, the (HSA-SOD-MTX) nanoparticles show super healing activity in rheumatoid arthritis in rats in comparison to other species″ [21].

Importantly, 100 characters (ninety-five p.f.c-Haps, five not genetic ones) are consistent to contain excellent suspected achievement through all six ML samples in non-visible test data collection of an expectation for MTX reaction in rheumatic articular disease patients. Most of these suspected p.f.c-Hap S.N.Ps are thought to be prominently active, also as part of genetic sites where p.f.c-Hap sets and are diagnosed as being related to previously recorded MTX and rheumatoid arthritis reactions [22].

The side events have been noticed even before the increased usage of MTX for rheumatoid arthritis patients since 1958. The majority of adverse effects of MTX involve gastrointestinal problems, pneumonitis, liver enzyme disorders, infections,

blood dyscrasia, renal injury and eczema. The fatal adverse events are rarely noticed through these optimal timing in the rheumatoid arthritis management of MTX due to its low dosage, but several complications may come with and lead to serious effects without relation to how much dosage is used such as liver injury, lung injury and bone marrow suppression. In conclusion, decreased damage and telling clients about real unwanted injuries may perform extra management efforts in rheumatoid arthritis patients. Newly published studies are usually hospital-dependent recordings of the effectiveness or harmfulness of MTX in the management of rheumatic articular disease with no systemic design up to the symptoms. So, this reading will assist the therapists and research workers in demonstrating the unwanted events of MTX usage in rheumatoid arthritis patients [17,23].

The usage of folic acid products with MTX treatment can stop the chance of unwanted effects. Finally, MTX is a potent DMARD, with a lesser occurrence of unwanted effects than other DMARDs and has a dose range which means that dosage can be calculated according to need [24]. MTX is widely used in the treatment of many disorders as; psoriasis, haematological malignancies such as acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, multiple myeloma, lymphomas and most notably, rheumatic articular disease [5].

The small-dose MTX (less than thirty milligrams weekly) is dependent on the cornerstone line of management of rheumatoid arthritis. Many actions and unwanted events of MTX differ by dose. Low-dose MTX works by reducing inflammation through increasing adenosine concentrations in the tissue, while large dosages of MTX (0.5 gm per m2 or more used intravenously) exhibit an antiproliferative cytotoxic action. At large dosages recommended for malignant diseases, dangerous injuries may elevate, but a small dose regimen seldom leads to life-threatening adverse effects [26].

The absolute contraindication of MTX is during pregnancy (category X) and lactation; females with gestation given MTX have a high chance of the 'aminopterin syndrome' described by fetal central nervous system (CNS), cardiac and skeletal anomalies [27].

The chance for liver injuries has been a major worry since the application of MTX (folate antagonist) for the management of rheumatoid articular disorders before the 1990s. Despite a ratio of important chance agents of hepatic injury already diagnosed, each chance clarification is kept non within the observing plan, involving the largely applied ACR recommendation, advised testing to evaluate for hepatic injuries at periods of at least 2-3 months in all RA patients managed with MTX, causing hepatic injury parameters, part of the commonest usual monitoring investigations in rheumatoid arthritis unit [28]. However, protection could be provided by using natural products and extracts, such as, silymarin [29] or anti-inflammatory corticosteroids methylprednisolone [30].

Conclusion.

Methotrexates provide important insight to the management of rheumatoid arthritis and mechanisms and actions could be fulfilled by introducing methotrexate at suitable time of the diseases stage and required dose is efficacious for outcome of the disease.

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