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Treatment of Rheumatoid Arthritis Based on Personalized Medicine: a New Approach in Rheumatology

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Abstract:
In the twenty-first century, there still needs more clarity on rheumatoid arthritis (RA). Rheumatoid arthritis is a widespread but heterogeneous illness with a broad range in its history, clinical symptoms, and response to therapy. It is now known that prevention of joint destruction, functional impairment, and a poor disease prognosis depends on early, correct diagnosis and starting therapy with disease-modifying drugs (DMARDs), among which methotrexate (MTX) remains the gold standard in the treatment of RA. Early rheumatoid arthritis diagnosis is crucial since it enables a speedier start to primary therapy. Pharmacogenetic and pharmacogenomic research, which aid in identifying a patient's genetic profile, may bring personalized treatment closer to reality. Identifying disease-specific genes while the organism's resistance to them is still intact should be made feasible by further study into RA.

INTRODUCTION

A diverse illness pattern that comprises its etiology, dynamics, course, and response to therapy will serve as the foundation for future medical practice. The guiding principle of personalized medicine is that, depending on the patient, the same illness might have a varied etiology, course, or treatment effectiveness. Consequently, it is essential to treat each patient as an individual (1).

In an era of unheard-of scientific and technical advancements, personalized medicine that emphasizes molecular diagnostics and estimating the risk of morbidity enables therapy to be tailored to each patient's requirements, increasing safety, efficacy, and cost-effectiveness. Personalized medicine is the antithesis of the conventional therapeutic method, which bases the therapy on reacting to observable symptoms of the illness. Personalized medicine is based on clinical, genetic, genomic, and environmental data unique for each patient. Personalized medicine is focused on giving the medication at the right time and in the right amount to each patient. The molecular study of not just certain illnesses but also of specific patients has made this approach practicable.

Additionally, the treatment preceded by pharmacogenetic testing is more successful since it enables the medication to be chosen based on a particular target. As a result, it is possible to predict how the patient's body will react to the medicine being administered. One benefit is increased efficacy, which is associated with a lower risk of adverse events (2). Additional advantages undoubtedly include ime saved and lower treatment costs (3).

According to the theory behind personalized medicine, diagnosing the disease at the molecular level makes it feasible to start treating patients while they are still in good condition. Genetic test results may be used to determine a person's propensity to acquire a specific illness. The relationship between genetic predisposition and increased or decreased illness risk determines how the disease will be managed. Therefore, preventive medicines should be provided to patients with a high chance of developing a disease. In order to prevent illness from developing, the patient's lifestyle should be changed (to get rid of undesirable behaviors), and regular testing should be performed (4, 5).

RA is a symptom, not a distinct illness.

RA is a long-lasting inflammatory condition affecting various joints' synovial tissue. The presence of high concentrations of acute-phase reactants, autoantibodies, and erosions on radiographs, along with the number of afflicted joints and the pattern of joint involvement, are used to make the diagnosis. Interestingly, patients with similar clinical symptoms and signs may exhibit quite different synovial leucocyte invasion and cytokine expression patterns.

There is evidence of variation in the genes linked to stromal cells, such as fibroblast-like synoviocytes, in addition to the considerable heterogeneity amongst RA patients about joint leucocyte invasion and activation of genes linked to inflammation (4, 5, 44).

Peripheral blood and synovial tissue exhibit inter-individual variation in the gene signature. For example, higher expression levels of IFN type I controlled genes have been found in the peripheral blood of nearly half of RA patients, which is compatible with the initiation of a pathogen-response program. The discrepancies between individuals with measurable anti-citrullinated peptide antibodies (ACPA) and people who are ACPA-negative substantially support the idea that RA should be seen as a syndrome comprising more than one pathogenetic entity (5, 44)

*Common final routes are impacted by efficient anti-rheumatic therapies*The fact that clinical arthritis activity is accompanied by persisting histologic evidence of synovitis after therapy with humanized anti-cluster of differentiation 52 (CD52) antibodies or chimeric anti-CD4 antibodies, despite substantial depletion of peripheral blood lymphocytes, serves as an illustration of the significance of gathering data on the synovium, the leading site of inflammation, to comprehend the effects of anti-rheumatic treatment (1, 43). Similarly, it has been demonstrated that B-lineage cells may remain in the synovium in some RA patients following rituximab treatment, even though nearly all patients significantly decrease peripheral blood B cells (2, 5, 44).

Successful use of DMARDs like gold, MTX, LEF, and CSs has consistently been linked to a reduction in the infiltration of mononuclear cells in the synovium. Like how rituximab, anakinra, and infliximab successfully treat RA patients, they also lower synovial inflammation. In one trial, patients were randomized to receive prednisolone therapy for two weeks using the COBRA regimen (Combinatietherapie Bij Reumatoide Arthritis) or a placebo. In this investigation, synovial sublining macrophages were shown to be the greatest biomarker for the clinical response to CSs. The efficacy of synovial macrophages as a possible biomarker was then evaluated across distinct therapies and kinetics (5, 44).

MEDICATIONS

Rheumatoid arthritis conventional therapy

The standard RA treatment plan comprises counseling, education, rehabilitation, and medication. Therapy aims to stop the pain, reduce or prevent inflammation, preserve normal locomotor function, delay or halt joint structural changes, and avoid organ abnormalities.

Pharmacological therapy for RA should begin as soon as feasible, ideally between 6–12 weeks after the onset of the initial symptoms. It should be successful in causing the illness to go into remission. The therapeutic window, defined as the period beginning no later than 12 weeks following the onset of the first symptoms, is the best indicator of remission (6). Patients with active RA should be checked every three months. If medication is not working, it should be changed no later than six months after starting it, according to the 2013 guidelines of the European League Against Rheumatism (EULAR).

The most crucial medications for treating RA are biological disease-modifying antirheumatic medicines (bDMARDs) and synthesized disease-modifying antirheumatic drugs (sDMARDs). Their goal is to prevent the sickness from spreading further. Nonsteroidal anti-inflammatory medicines (NSAIDs), glucocorticoids (GCs), and analgesics treat illness symptoms but do not stop the disease's progression. Figure 1 (7) illustrates the pharmacological treatment plan for rheumatoid arthritis.

Tofacitinib is a medication of the newest generation. In cases of moderate to severe symptom severity, it is used to treat active rheumatoid arthritis. This medication is marketed in 20 nations, notably Mexico,

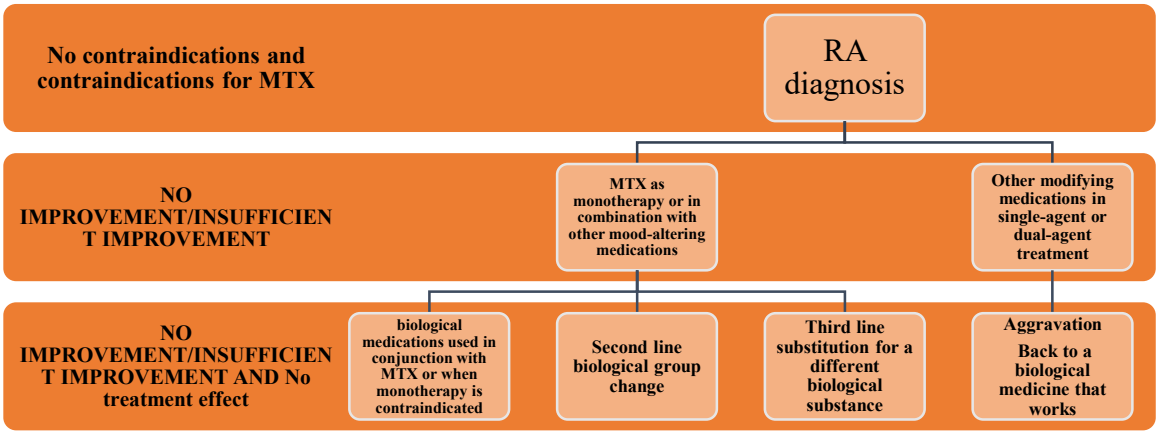

Fig 1. The regimen for treating RA with medication. Source: Original research based on EULAR suggestions (7).

Argentina, Japan, Switzerland, Russia, and Turkey. However, the European Medicines Agency has yet to approve it (EMEA). Tofacitinib must be accepted before it may be used in Poland and other EU nations.

Medications that are non-steroidal anti-inflammatory

These medications significantly shorten the length of morning stiffness and the discomfort associated with the disease's symptoms. According to European Guidelines from 2011 (8), the medication should be customized for each patient based on their potential for coronary or gastrointestinal problems.

Glucocorticoids

Glucocorticoids (GCs) and DMARDs are suggested as a first-line therapy approach in the 2010 EULAR guidelines. In the event of illness exacerbation, they are given for a brief time at greater dosages and modest doses (10 mg/day) (9). However, it should be emphasized that new research indicates that long-term usage of glucocorticoids in RA raises the chance of a heart attack by 68%; as a result, each patient's need for their administration should be carefully considered. The chance of having a heart attack after taking GCs relies on the dose, which rises by 13% with every 5 mg increase in dosage, and the period of usage, which rises by 10% annually (10). The 2013 EULAR guidelines for managing rheumatoid arthritis advise using glucocorticoids in lower dosages at the beginning of the illness and pairing them with DMARDs for no more than six months, if feasible (10).

Analgesics and pain management

The Visual Analogue Scale (VAS), the Numerical Rating Scale (NRS), and the Verbal Rating Scale should all be routinely used to measure pain in patients with arthritis, according to the recommendations of international experts in the field of rheumatology from the 3E Initiative (Evidence, Expertise, Exchange) (VRS). In the event of persistent pain, paracetamol is advised for arthritis sufferers, as is paracetamol mixed with nonsteroidal anti-inflammatory medicines. Neuromodulators that affect how pain signals are received, as well as tricyclic antidepressants, may be used to treat patients with inflammatory rheumatic illnesses. Benzodiazepines with muscle relaxants, often known as muscle relaxants, should not be used. When standard treatment fails, weak opioids may be given for a brief time. Weak opioid usage over an extended period is an option, but this treatment calls for ongoing care. Only extreme circumstances should call for potent opioids like morphine and its analogs (11).

Anti-rheumatic medications that treat disease

Synthesized anti-rheumatic medications that treat illness

Methotrexate (MTX), sulfasalazine (SSZ), leflunomide, and, in rare circumstances, azathioprine, cyclosporin A, and cyclophosphamide are examples of synthetic disease-modifying anti-rheumatic medications.

Methotrexate: Immediately upon diagnosis, methotrexate, a medication used in the initial therapy approach for RA, should be suggested. Once a week, 20–30 mg of MTX is the recommended dosage. Starting at 10-15 mg, the dosage should be raised to 20-30 mg by adding 5 mg every 2-4 weeks. Tetrahydrofolate is decreased by methotrexate via blocking dihydrofolate reductase. It prevents the metabolism of purines and pyrimidines and the creation of nitrogenous bases like thymidine. Additionally, methotrexate reduces cell growth, boosts T cell apoptosis and endogenous adenosine levels, and modifies the expression of intercellular adhesion molecules, all of which have an effect on the suppression of pro-inflammatory cytokine production and cellular response. Neutrophils, macrophages, monocytes, and dendritic cells are inhibited in their ability to cause inflammation by methotrexate.

The rise in aminotransferases activity (10-43%), gastrointestinal symptoms (20-65%), stomatitis (10-15%), anemia (10-15%), leukopenia (12%), and thrombocytopenia (12%) are among the most frequent adverse effects of MTX. Less often encountered conditions include central nervous system dysfunction (8–10%), hair loss (8%), bronchitis (2.1–8%), infectious diseases (5%), and subcutaneous lumps (2–6%) (12).

The severity of methotrexate hepatotoxicity in elderly RA patients varies with the length of treatment. Cirrhosis only affects 0.1% of individuals, but benign hepatic fibrosis affects around 7% of people. Before starting MTX treatment, the following tests should be run: liver transaminases (AST, ALT), ammonia, albumin, blood counts, and blood smears. Testing for HBsAg and HCV antibodies and a chest X-ray should be done to rule out hepatitis B and C infection. Additional options include HIV testing, glucose measurements, lipid profiles, and pregnancy tests. Control tests (AST, ALT, blood count, blood smear, and creatinine concentration) should also be performed during MTX treatment; first, every 4-6 weeks and then every 1-3 months after the target dosage has been reached. Because MTX is teratogenic, fertile women should utilize an effective means of contraception. The treatment must be stopped in women and men three months before the anticipated pregnancy. Women who are expecting or nursing cannot take methotrexate (13).

Sulfasalazine: When MTX cannot be taken or in conjunction with other medications, sulfasalazine is advised for rheumatoid arthritis treatment. Bacteria in the colon break down sulfasalazine into its two

primary metabolites, sulfapyridine, and mesalazine (5-aminosalicylic acid). SSZ's treatment of RA still needs to be fully understood. According to current research, it suppresses the production of cell adhesion proteins in leukocytes and epithelium and creates antibodies in reaction to antigen stimulation. 2-4 g/day is the therapeutic dosage for RA.

Leflunomide: Leflunomide is a prodrug whose action is dependent upon an active metabolite (A771276) produced by metabolism in the liver and intestinal walls. A771276 has a half-life of around two weeks. Interleukin 2 (IL-2) production, tumor necrosis factor (TNF) activity, antibody generation by B lymphocytes, T lymphocyte proliferation, and the migration of inflammatory cells to the synovial membrane are all inhibited by leflunomide. Leflunomide's loading dosage is one 100 mg tablet daily for the first three days of therapy. Next, a maintenance dosage of 10 to 20 mg per day is administered (depending on the severity of symptoms).

Biological disease-modifying antirheumatic drugs

Biological drugs are recommended when synthetic DMARDs (MTX in particular) have proved to be ineffective and the disease remains active. Contraindications for application or side effects of DMARDs are another reason to use biological drugs. Tumour necrosis factor α inhibitors were the first biological drugs used in treatment of rheumatoid arthritis. At present in Poland the following drugs are registered and qualified for therapeutic programmes of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA): infliximab, etanercept, adalimumab, certolizumab pegol, golimumab.

Biologically based anti-rheumatic medications

When synthesized DMARDs (MTX in specific) have shown to be unsuccessful, and the illness is still active, biological medications are advised. Another justification for using biological medications is the presence of DMARD side effects or application contraindications.

Inhibitors of tumor necrosis factor were the initial biological medications used to treat rheumatoid arthritis. For therapy programs for rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA), the following medications are now approved in Poland: infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab.

Tocilizumab: Tocilizumab is a genetically engineered humanized monoclonal IgG1 antibody that binds exclusively to the membrane-bound and soluble interleukin-6 receptor (IL-6R) and blocks the signal transduction process by both mIL-6R and sIL-6R. 8 mg/kg of it is injected intravenously every four weeks. It is advisable to provide a dosage of less than 800 mg/infusion to individuals who weigh more than 100 kg. Both monotherapy and combination treatment with MTX is possible when using tocilizumab. The half-life of each 8 mg/kg dosage given every four weeks is between 8 and 14 days.

Abatacept: Abatacept is a soluble recombinant fusion protein made up of a human T cell-bound extracellular portion of antigen 4 (CTLA-4), linked to the immunoglobulin IgG1's modified Fc region. Abatacept blocks CD80 and CD86 molecules by attaching to CD80/86 receptors on antigen cells, which results in a reduction of the stimulating effect of CD28 protein on T cells. The recombinant DNA technique makes abatacept in Chinese hamster ovarian cells. 10 mg/kg/month is given intravenously between weeks 0 and 2, then every four weeks after that. Abatacept has a final mean half-life of about 13 days and is utilized in combination treatment with MTX or other DMARDs.

New biomarkers are required for a novel approach to managing rheumatoid arthritis

Rheumatoid arthritis still has a bad reputation in the twenty-first century. Its history, clinical symptoms, and clinical response to therapy make RA a prevalent yet varied illness. In order to avoid joint degeneration, functional impairment, and an unfavorable course of the illness, it is now understood that an early, accurate diagnosis and initiation of DMARD therapy—of which MTX represents the standard method in managing RA—are essential (14).

Patients with RA with MTX treatment failure due to toxicity or lack of effectiveness are shifted to other therapeutic choices to choose the most beneficial. Multiple ineffectual treatments come at a significant expense and may have unfavorable consequences, and it is not always feasible to have good treatment results. The right choice of a safe and effective treatment may be a useful instrument not only for treating disease symptoms (such as tiredness, joint pain, and swelling) but also for preventing joint damage, extending and improving quality of life, and even the remission of the illness. Unfortunately, even though MTX and biologic medicines typically lead to a better prognosis for RA patients, up to 40–60% of these patients fail to get a sufficient response, and 15–30% of them experience adverse medication reactions (15, 16).

Although the cause of this individual variation is unknown, studies have been able to uncover biomarkers indicative of therapy response. In the context of personalized therapy, it is inadequate to employ conventional indicators that have proved clinically helpful, including autoantibodies, acute phase reaction conditions, bone and cartilage indicators, and different cytokines (17). Therefore, according to biologists and

rheumatologists, finding new, improved biomarkers would help us understand the molecular processes involved in the pathogenesis of the illness and better choose the best medications for first-line therapy. Serum biomarkers such as proteins or microRNAs and analysis of gene profiles and gene expression patterns are likely to be more beneficial than static gene panels. We think that only by taking extensive steps to uncover biochemical, clinical, and genetic/epigenetic indicators that assist us in comprehending the many causes for focused therapy would we be able to accomplish good treatment (Fig. 2). Several variables likely influences the reaction to the effectiveness and toxicity of the treatment. However, genetic/epigenetic predisposition is one of the most significant. These biomarkers may be helpful in routine practice since they are not affected by the passage of time and may be analyzed using blood samples from patients (18). The therapeutic tactics, which are no longer a linear process, are also impacted by the understanding of the molecular basis of the illness, as is the integrated system known as the "knowledge management system," which combines clinical data from one patient with molecular and pharmacogenetic data.

Pharmacogenetics' role in genetic investigations

Genetic variations may affect illness vulnerability, disease progression, or a person's reaction to treatment, which has been shown for more than 40 years (19). Additionally, they offer many advantages over other markers, making them particularly appealing biomarkers owing to the standardized assays and linkages used to discover and confirm tests (20). In the last ten years, several studies have shown that single-nucleotide polymorphisms (SNPs) in genes that regulate the metabolism, transport, and action of pharmaceuticals may affect both the toxicity and the effectiveness of treatments (21–24).

The genes implicated in the pathophysiology of rheumatoid arthritis and the inflammatory signaling system were chosen as the candidate genes for genetic variation analysis (24). Although several SNPs are related to treatment response in RA patients, the bulk of these results still needs to be tentative and consistent. They are restricted to recognized genes implicated in the cellular pathways of DMARDs and biological drugs (21, 23). Size of samples (typically too small, n 1000), amount of SNPs in drug target genes, variations in immigrant communities, population stratified, biological background for tested populaces, variations in clinical features of patients, variations in disease stages, prior drug history, and finally variations in study design may all be contributing factors to the discrepancy (18, 23). Genome-wide association studies (GWAS) may be a more effective method for selecting potential genes for inclusion in these pharmacogenomic models since numerous genes, not just one, are implicated in the etiology of RA and medication responses (15, 22). GWAS is a practical, hypothesis-free way to find common disease-associated SNPs prevalent in the general population, scanning hundreds of thousands or millions of polymorphisms throughout the whole genome for each person (18, 25). The success of GWAS has revealed the complex genetic architecture susceptibility and opened up a sizeable new field for investigation (19). The results from GWAS and the biochemical and clinical connections between the particular loci and illnesses should be further investigated by conventional candidate gene investigations, such as allelic discriminating by TaqMan real-time PCR (18, 25). This is because GWAS do not identify the link between a gene and the disease phenotype. New methods, like next-

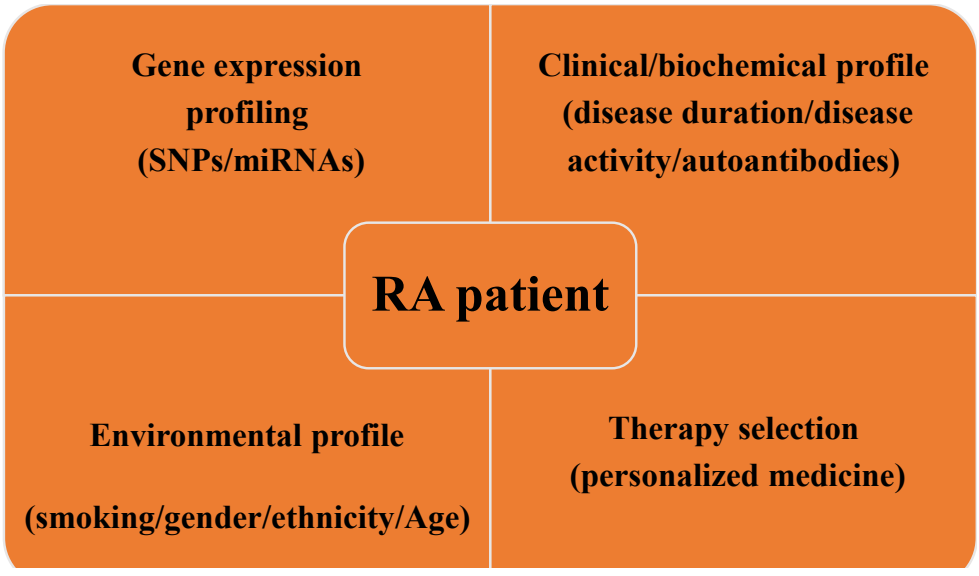

Fig2. Procedure for RA patients› treatment optimization.

generation sequencing (NGS), which are not restricted to gene chips and allow the discovery of common and uncommon variations influencing the response to medications or adverse drug responses, are being developed in addition to GWAS (18). Data produced utilizing NGS technology, which has high sensitivity and bandwidth qualities, is more persuasive than that obtained using GWAS.Furthermore, both fundamental and clinical investigations benefited greatly from the NGS analysis. Additionally, the identification of causal gene loci allows us to pinpoint elements connected to RA's pathogenesis and the effectiveness of treatment. One of the crucial stages in understanding the etiology of polygenic illnesses is gene identification. However, the research mentioned above showed that genetic variations (located in the promoter, regulatory, or coding regions of the relevant gene) contribute significantly but insufficiently to the risk of developing RA. The creation of novel intervention techniques will be made feasible by gene-expression profiles and epigenetic alterations, which are generally acknowledged to offer an extra window for understanding the potential pathways that contribute to the pathogenesis of RA.

Pharmacogenomics: the profiling of gene expression

In rheumatology, the concept of "personalized or precision" medicine, which permits the future use of genetic data for a logical choice of treatment to optimize health outcomes while reducing adverse effects, is a natural development of the knowledge we have accumulated over the years few decades. Gene-expression profiling, which examines how genes are expressed or activated, is a molecular fingerprint that has enormous promise for RA pathopathogenesis research as well as patient management and individualized therapy planning (16, 26).

Many human transcripts only express partially during a particular stage of illness, according to research on the measurement of gene expression in various tissues or situations (18). Genetic variations in regulatory elements, such as cis-expression quantitative trait loci (eQTL), which are likely active on the same chromosome, or trans-eQTL, which act on distant genes on non-contiguous chromosomes, may affect the abundance of a gene transcript (18, 27). With eQTLs, it is possible to link polymorphisms with unknown functions whose higher expressions are linked to complex traits due to pleiotropy (28, 29).

In order to comprehend the biology of RA illness and possible medication development pathways, this technique enables the discovery of correlations between genes and areas linked with the risk of RA. Genome-wide gene expression analysis using cDNA microarrays has become a powerful technique that may be used to find genes that may be biomarkers for the detection and surveillance of disease severity (30, 31). This is because genes regulate their biological functions in groups rather than alone. Because hundreds of genes were examined and expression profiles were associated with medication responses, cDNA microarrays allowed for a more thorough investigation of drug reactions. The small size of cohorts and the dynamic phenotype of RA are significant barriers to identifying reliable biomarkers. They are why prognostic and diagnostic microarrays have not been established and clinically applied, even though microarray analysis has led to identifying a gene signature that distinguishes the phase of RA and the response to therapy. NGS is currently challenging arrays as the preferred technique for genome analysis since it offers various benefits over microarrays, such as vast parallel RNA sequencing, identification of non-coding transcripts, and alternative splicing processes (16).

After all, the scientific community uses microarrays, and there are established bioinformatics processes to interpret array data. When the DNA or RNA of several specimens, such as strains isolated, has to be probed or when a low-cost "fast glance" is necessary, microarrays may be helpful as a screening tool. However, NGS might be utilized to offer thorough deep-sequence analyses of genomic DNA to detect alterations after specimens of interest are identified (32). Genome-wide methods such as NGS and microarray analysis may increase the overall survival of RA patients and increase the accuracy of diagnosis and therapy response prediction. Additionally, there are compelling arguments in favor of using a similar strategy to enhance the treatment of individuals with rheumatic disorders, given the successful use of gene-expression profile data in clinical usage in cancer.

Pharmacogenomics using microRNA profiling

The level and function of a protein may be affected by genetic polymorphisms not just in the promoter, regulatory, or coding sequence of the relevant gene, which can modify how a protein is expressed. It is commonly acknowledged that essential tasks in the control of gene expression need epigenetic processes like DNA methylation or microRNA (miRNA, miR). Additionally, recent research has shown that miRNAs are novel pharmacogenomics indicators for anti-rheumatic medications, and epigenetic aberrations are emerging as critical pathogenic aspects of rheumatoid arthritis (33). Small, noncoding RNA molecules called miRNAs tightly control biological processes by modulating protein levels at the posttranscriptional level. They comprise roughly 1-2% of the whole genome (34–36).

They serve essential immune response controllers in both healthy and diseased circumstances. In the past,

miRNAs were thought to control gene expression inside the cell. MiRNAs, however, are emerging as new candidate biomarkers for diagnosis and prognosis in a variety of diseases. These disorders, including RA, may be detected directly in organs and biological material by polymerase chain reaction (PCR) or array technology and are stably present in a cell-free state in bodily fluids like plasma or serum. In the last two years, it has been proposed that miRNAs impact the immune cell niche and regulate cellular metabolism (35). A few miRNAs were up-regulated in both plasma/serum liquids and inflamed joints; abnormal miRNA expression in individuals with rheumatic illnesses was initially described less than ten years ago (34, 35).The miRNAs are reportedly expressed even at various phases of disease development; they may also help monitor RA severity and understand its pathophysiology (33). MiR-16, -132, -146, and -155 have been revealed to have a role in regulating the growth and operations of rheumatoid-associated cells (34). MiR-146 and miR-155, which are involved in forming innate and adaptive immune cells, are crucial for maintaining immunological homeostasis and are up-regulated in inflammatory conditions. These two miRNAs in RA patients have been the subject of the most research (34, 35). Due to the negative correlation between plasma levels of the miRNAs mentioned above and disease activity measures, they serve as biomarkers for RA activity that may be helpful for therapy monitoring (DAS-28, VAS, number of tender joints (34). Although a few miRNAs contribute to various RA pathogenesis and have solid therapeutic potential, specific miRNA signatures in RA have yet to be identified. However, miRNAs can control many immunological pathways and function as messengers for cell-to-cell communication, making them perfect candidates for therapeutic development. Because of this, it is now clinically feasible to look for particular expression profiles of miRNAs in RA patients for prognostic/diagnostic reasons (34).

Therefore, therapeutically controlling miRNA levels may open up new avenues for optionally controlling the immune system and delaying or halting the course of illness. Compared to conventional pharmacological treatments, miRNA-based therapies offer a few advantages: they are a class of highly effective and selective regulators, and one miRNA may control many genes simultaneously, impacting numerous signaling pathways (35). However, a greater understanding of the roles of the previously and recently found miRNAs is required before we can envision the development of miRNA-based therapeutics for the treatment of RA.

There is a genetic test for rheumatoid arthritis.

Millions of RA sufferers take medicines every day that are useless to them. Early rheumatoid arthritis diagnosis is essential since it allows for a quicker start to the primary therapy. Pharmacogenetic and pharmacogenomic research, which helps identify a patient's unique genetic profile, may advance personalized medicine. Rheumatologists still hope to find precise biomarkers for diagnosing and treating RA. Unfortunately, pharmacogenetic/pharmacogenomic testing is not widely used nowadays. This may be the result of several factors, including the heterogeneity of RA, incomplete knowledge of the disease's pathogenesis, a small sample size, and other non-genetic factors (demographic, environmental, and clinical or serological markers) that can affect or predict a drug's efficacy or toxicity in RA patients.

Furthermore, there are several reasons why it is crucial to pinpoint the specific genes and epigenetic modifications responsible for the onset, progression, and therapeutic response to rheumatoid arthritis. These include forecasting who will acquire RA, estimating the severity of the condition, predicting how an individual with RA will react to therapy, and discovering novel therapeutic targets. Identifying how genetic/epigenetic changes impact the biochemical function in specific cell subtypes and are related to RA susceptibility and severity will be one of the biggest problems for researchers in the following years. Integrating the most recent findings from genetic testing into clinical practice by creating assessment tools that benefit from personal genomic/epigenetic information (18). Recent developments in cutting-edge technology, like NGS, could provide a more individualized approach to patient practice, with improved risk classification and treatment options based on data from a unique genetic/epigenetic background (18). Though companion diagnostics may not be cost-effective, pharmacogenetic/pharmacogenomic approaches may be costly due to the high cost of biologic therapy for RA patients. Additionally, identifying the genetic/epigenetic elements behind the variation in medication treatment responses may help identify responder and non-responder individuals early, encouraging the development of better and more efficient therapeutic approaches for rheumatoid arthritis patients.

Therapy selection

Treatment can be tailored based on variations in treatment response and clinical phenotype-based personalization. The best impact lasts at least 6 to 12 weeks, so selecting the proper DMARD medication is crucial to achieving the suggested therapeutic objectives. As a result, it is best to forecast the outcome of the therapy before it begins. Future rheumatologists will likely use biomarkers to guide their treatment decisions, particularly when deciding between bDMARDs and tsDMARDs. For instance, Tao et colleagues utilized machine learning to

create models based on gene production and DNA methylation information to forecast how RA patients will respond to adalimumab and etanercept. When utilizing gene expression, they obtained a response prediction accuracy of 84.7% (adalimumab) and 88% (etanercept), and when using DNA methylation, they reported reliability of 85.9% (adalimumab) and 79% (etanercept) (45).

Future of personalized medicine

The likelihood that rheumatoid arthritis may proceed to pathology decreases the sooner the correct diagnosis is obtained. Further research into RA should make it possible to identify disease-specific genes while the organism's resistance to them is still intact (before auto-aggression develops). Future research should focus on understanding how tolerance is broken in spatiotemporal in vivo networks with the benefit of rationalizing current treatments or giving the correct patient the proper medication at the right time and place (37).

Because around one-third of RA patients do not react to a particular biological treatment, tailored medicine is crucial for RA patients. The progression of RA is quite complex. This likely explains why every patient responds to therapy differently (38). Studies conducted on RA patients do not account for distinct pathotypes responsible for therapy response. According to British research, a poor response to TNF inhibitors and a high degree of impairment in the RA patient population are strongly correlated (39).

Lack of concurrent treatment with MTX or non-steroid anti-inflammatory medications reduces the likelihood of response, particularly to etanercept. Also seen in the group of women is a lower likelihood of remission. Swedish trials' findings show that individuals treated with DMARDs and with a lower degree of impairment have better success in TNF inhibition. The results of the Danish investigations, however, indicate that older patients and those who had prednisolone had a lower response to the initial anti-TNF medication (39).

Future customized therapy for rheumatoid arthritis should be based on a "composite grading system" based on several biomarkers and demographic data. Consequently, the symptoms might adapt to each patient's therapy individually. This will lessen adverse effects, enhance results, and save expenditures. Studies comparing various biological treatments "head-to-head" that can suggest the best therapeutic choice is progressively taken into account. For instance, some study findings suggest that tocilizumab may be a better initial option for individuals who cannot tolerate MTX while receiving biological treatment. These data must, however, be evaluated in light of the carefully chosen clinical trial group (38).

Anti-citrullinated protein antibodies are used in new diagnostic criteria for rheumatoid arthritis that have been developed (ACPA). The next stage is identifying the indicators that may be utilized to discriminate between RA and undifferentiated arthritis. The discovery of biomarkers at this time and the creation of tools that include biomarkers and stage-related clinical features will influence the beginning, choice, and length of therapy (40). Early diagnosis and prompt treatment are crucial for inducing remission and preventing irreparable damage to the joints in rheumatoid arthritis. Preferably, an initial detection should be made during the asymptomatic or pre-clinical stage. According to several studies, the rheumatoid factor (RF) and ACPA were both present before the onset of RA (41).

In clinical practice, tests that measure well-known diagnostic biomarkers are often utilized. According to estimates, the outcomes of these tests form the basis of 70% of the treatment choices made by doctors. However, integrating new biomarkers into medical care has proven to be a protracted and challenging process involving persuading doctors. A crucial stage in ensuring the biomarker's adoption in medical care and further improvement of its usage is evaluating its effect on general health. As biomarkers are used more often in clinical practice, this study topic is becoming more and more significant. The complexity and heterogeneity of rheumatoid arthritis make it unlikely that a particular cytokine could distinguish between different types of the disease well enough. Several trustworthy multiplex cytokine tests are now leading in this field (although, in the case of RA, it may not be an appropriate solution due to RF interferences). Since tests are helpful in the treatment of other illnesses, implementing them in rheumatology should be simple (technically). However, it is essential to define the precise performance definition and quality control for the relevant cytokines in RA. The disease's intricacy now constrains RA as it relates to cytokine networks. Future customized treatment for RA may take a more practical approach if it uses various biomarker profiles based on genetic and proteomic markers. A multivariate study like this one could show trends rather than specific biomarkers. A single IL-7 may predict diagnosis in the early stages of the illness. However, a more complicated mix of markers may be required to predict the response to treatment and identify subgroups of individuals with more progressive disease (42).

CONCLUSION

In order to increase responsiveness, maintain the structural and functional characteristics of the joints, and lower treatment costs, there is a critical need for reliable biomarkers that relate to the reaction to

biological therapy. According to certain studies' findings, it is now possible to forecast how effectively rituximab will work as a therapy because of various clinical traits related to how the body will react to TNF suppression and the existence of antibodies in the blood. A lack of reaction cannot be foreseen, but current response markers may forecast the likelihood of response to a medicine or the quality of response. Antibodies play a significant role in the new ACR/EULAR clinical definition for rheumatoid arthritis. Including seropositive individuals in RA cohorts in the future cannot be ruled out. So far, treating patients with seronegative RA with another drug makes sense before starting them on rituximab (39, 43).

Before molecular illness diagnosis—the cornerstone of the tailored approach—becomes the norm, personalized medicine must address three fundamental problems. The first and most crucial problem is the need to test one million single nucleotide polymorphisms (SNP) that are present in the genome to determine genetic diversity is the first and most crucial problem. The SNPs that cause the illness and may serve as therapeutically useful indicators should next be identified. Another concern would be money-related issues. Only costly genotyping techniques and a thorough grasp of biological defense processes make it feasible to search for disease indicators. Another problem is that protein markers are challenging to type since there is restricted access to the proper tissues in the case of numerous disorders. For this sort of data analysis to be successful, both proteomic and computational technologies need additional development.

Finding reliable biomarkers, such as genetic markers, is necessary to forecast uncommon adverse occurrences. These markers ought to be capable of being detected in small samples. However, there is precedence for this. For instance, thiopurine S-methyltransferase genetic polymorphism and azathioprine-induced bone marrow reduction (40) or liver toxicity from flucloxacillin and HLA-DRB*5701 (OR > 80) are examples.

Biomarkers must be found and verified to apply for tailored medicines as effectively as feasible. Therefore, it is necessary to create new rules that outline how industry and academics interact regarding regulatory oversight.

New norms for stakeholders participating in all phases of the implementation of personalized medicine must also be developed, from the validation of biomarkers to the patient's informed consent. Various barriers are preventing customized medicine from being widely adopted. The actual example is the need for specified norms of behavior and stakeholder participation and the inappropriateness of European financing policies and data availability. Another obstacle to the adoption of customized medicine is the healthcare system. These issues can and ought to be successfully resolved. Systematic steps must be promptly done to overcome obstacles to customized medicine's implementation in order for it to be used successfully (44).

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