Artificial Intelligence and Prediction of Response to Biologics in Psoriatic Disease Using Immunophenotype Data: A Mini Review

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ABSTRACT Over the last decade the use of artificial intelligence (AI) has reformed academic research. While clinical diagnosis of psoriasis and psoriatic arthritis is largely straightforward, the determining factors of a clinical response to therapy, and specifically to biologic agents, have not yet been found. AI may meaningfully impact attempts to unravel the prognostic factors that affect response to therapy, assist experimental techniques being used to investigate immune cell populations, examine whether these populations are associated with treatment responses, and incorporate immunophenotype data in prediction models. The aim of this mini review was to present the current state of the AI-mediated attempts in the field. We executed a Medline search in October 2023. Selection and presentation of studies were conducted following the principles of a narrative–review design. We present data regarding the impact AI can have on the management of psoriatic disease by predicting responses utilizing clinical or biological parameters. We also reviewed the ways AI has been implemented to assist development of models that revolutionize the investigation of peripheral immune cell subsets that can be used as biomarkers of response to biologic treatment. Last, we discussed future perspectives and ethical considerations regarding the use of machine learning models in the management of immune-mediated diseases.

IMAJ 2024; 26: 114–119

KEY WORDS: artificial intelligence (AI), flow cytometry, machine learning (ML), psoriasis, psoriatic arthritis

Psoriatic disease is a chronic immune-mediated inflammatory disease that afflicts 2% of the population worldwide and manifests itself in a variety of clinical forms. It is a heterogeneous condition that affects skin and frequently (in about 30% of patients) axial joints and entheses [1]. The unique characteristics of the disorder significantly impact quality of life.

Over the last decade the use of artificial intelligence (AI) has reformed and revolutionized academic research. Machine learning approaches have been implemented to identify the diagnosis of psoriasis [2,3], to assess severity of psoriasis [4], to classify the type of the disease [5], and to predict the risk for development of psoriatic arthritis [6]. AI tools have also been used to aid the recognition of undiagnosed patients with psoriatic arthritis [7]. Recently, a machine learning model pre-identified undiagnosed patients with psoriatic arthritis in a psoriasis cohort and a general population cohort with a specificity of 90% and 99% respectively, 1 to 4 years before patients were suspected of having psoriatic arthritis [7]. The nascent field of utilizing AI in medicine is expected to grow fast and eventually transform clinical practice.

While clinical diagnosis of psoriasis and psoriatic arthritis is largely straightforward, the determining factors of a clinical response to therapy, and specifically to biologic agents, have not yet been found. A therapeutic decision is largely based on a trial-and-error approach. At the same time, studies characterizing the peripheral immune populations of the patients have revealed that different immunophenotypes are associated with different disease severities and responses to therapy. AI may meaningfully impact attempts to unravel the prognostic factors that affect response to therapy, assist experimental techniques being used to investigate immune cell populations, examine whether these populations are associated with treatment responses, and incorporate immunophenotype data in prediction models [Figure 1] [8]. AI has become an increasingly used tool both in terms of diagnosis and management but research articles on this topic fail to provide an overview for those unfamiliar with the complex nature of the types of models being used, which could be used to familiarize non-experts such as rheumatologists

or treating physicians. The aim of this mini review was to present the current state of the AI-mediated attempts in the field.

METHODS

We searched MedLine using PubMed for articles published before October 2023. We utilized terms such as *psoriasis*, *psoriatic arthritis*, and *artificial intelligence*. The search string used was: (psoriasis OR (psoriatic AND arthritis)) AND (artificial[title] OR machine learning[title] OR intelligence[title] OR AI[title]). Selection and presentation of studies were executed following the principles of a narrative-review design. Results presented are prone to selection bias, as in every narrative review.

BY IDENTIFYING KEY IMMUNOPHENOTYPE PARAMETERS AND PATHOLOGICALLY SIGNIFICANT CELL SUBSETS, AI CAN PAVE THE WAY FOR NOVEL BIOMARKERS AND THERAPEUTIC TARGETS.

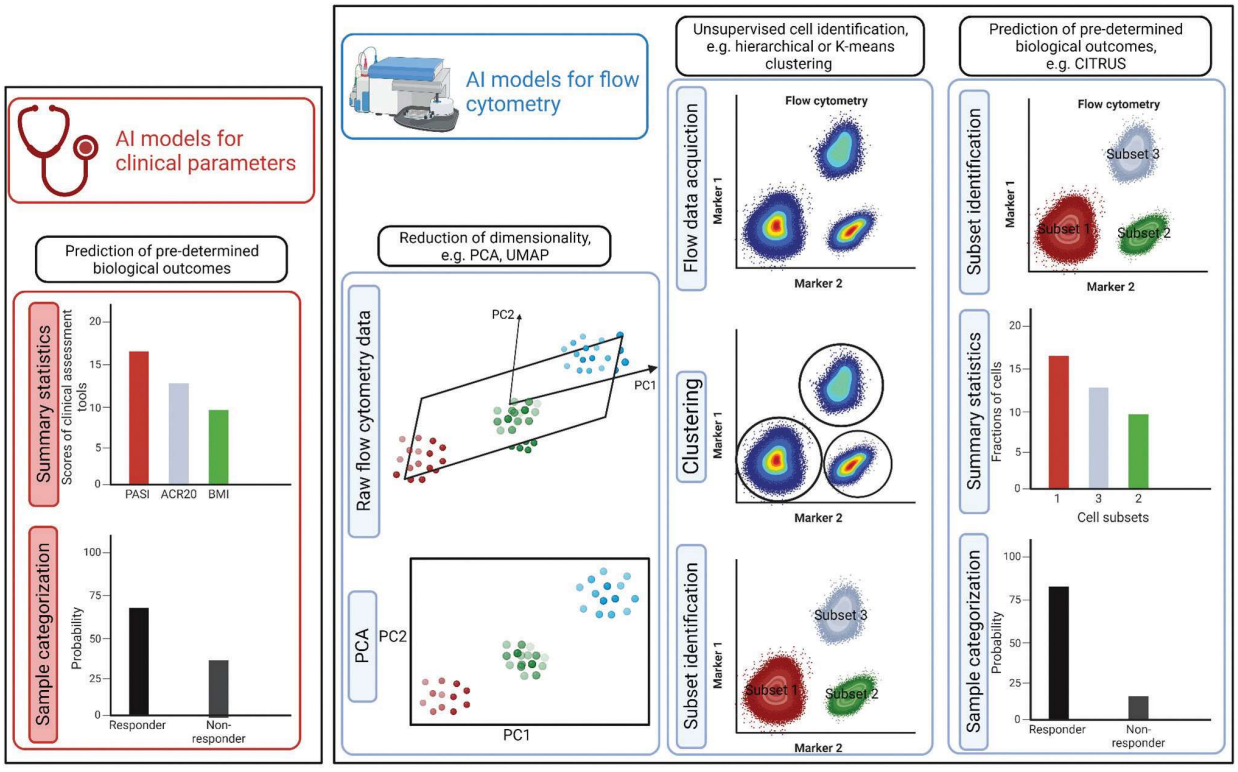
BRIEF OVERVIEW OF TYPES OF MACHINE LEARNING MODELS

To accommodate a better understanding of this review for non-experts, we provided an overview of the types of machine learning models (e.g., supervised learning, unsupervised learning) in a concise way. Nevertheless, a detailed review of the methods utilized to develop the models is not the subject of this text. It is important to note that the choice of the model and the handling of data are critical in developing predictive models using immunophenotype data. The complexity of biological systems and the variability in individual responses necessitate careful consideration of these aspects to develop robust and reliable predictive tools.

Supervised learning refers to models that are trained on labeled data. For example, a dataset where patient profiles (including their immunophenotype data) are labeled with their responses to specific treatments (e.g., responsive, non-responsive). Algorithms such as logistic regression, decision trees, random forests, and support vector machines can be used here.

Unsupervised learning models identify patterns in data without predefined labels. Clustering algorithms like K-means or hierarchical clustering can group patients based on similarities in their immunophenotype profiles, potentially revealing subgroups that respond similarly to certain treatments.

Figure 1. Applications of artificial intelligence (AI) in psoriatic disease-related prediction (Preparation by Biorender licenced to DPB)



Deep learning refers to neural networks that can handle complex, high-dimensional data and can uncover intricate patterns. Convolutional neural networks or recurrent neural networks might be used if the data has spatial or sequential patterns.

Reinforcement learning could be explored in dynamic treatment regimens where the model learns the best treatment strategy by continuously improving through trial and error, although it is more complex and less common in this field.

AI-ASSISTED TOOLS

Predicting response utilizing clinical parameters

One approach in creating treatment-response predictors is building AI models that utilize clinical parameters that are easy to measure in clinical practice. For example, prediction of long-term effectiveness of biologics in patients with psoriatic skin manifestations utilizing clinical data, such as the sex, age, body mass index, co-morbidities, and disease severity (psoriasis area severity index) as well prior treatment exposure has already been achieved. Researchers managed to accurately calculate the likelihood of discontinuation in the first 5 years after treatment initiation [9]. Moreover, another group has suggested that an algorithm was able to predict the probability of remission in patients diagnosed with psoriatic arthritis who were treated with secukinumab, an anti-IL-17 monoclonal antibody, and identify good responders. Patients with fibromyalgia or axial disease were deemed as less likely to maintain a 12-month remission [10]. A third research team reported that by using machine learning approaches they were able to identify patients who exhibited a small chance to withdraw from treatment [11]. Gottlieb and colleagues [12] used a Bayesian elastic net to characterize patients with psoriatic arthritis who were more likely to benefit from a secukinumab 300 mg starting dose over a secukinumab 150 mg starting dose. Moreover, psoriatic arthritis phenotypes that are associated with better response to guselkumab have also been identified using machine learning techniques on data from the DISCOVER-1/DISCOVER-2 clinical trials [13]. Similarly, the profile of fast responders that accurately predicted secukinumab response in patients with psoriasis was also described using artificial neural networks [14]. Last, Pournara et al. [15] utilized baseline data of patients with psoriatic arthritis who had been enrolled in randomized controlled trials. Using a finite mixture models methodology, they described patient clusters that were more likely to improve from a secukinumab 300 mg regimen compared to a secukinumab 150 mg one.

ENSURING EQUAL ACCESS TO DATA AND ADVANCED AI TECHNIQUES IS PARAMOUNT TO PREVENTING A WIDENING HEALTHCARE DISPARITY GAP.

Predicting response utilizing biological parameters

Another approach of AI-assisted prediction-tool-construction is to incorporate non-clinical parameters. Identification of additional disease-specific biological variables, not clinical ones, that add predictive value to such approaches will eventually shape even more accurate prediction models. For example, models utilizing blood protein data (such as the levels of IL-17A and IL-17C) have also been tested for patients with psoriatic disease. The models were able to predict a clinical endpoint after 12 weeks of treatment with tofacitinib, a JAK inhibitor, or etanercept, a fusion protein of the tumor necrosis factor-α (TNFα) receptor, highlighting the critical role of integrating biologic variables to develop meaningful response predictors [16]. Interestingly, trained classifiers using combined tofacitinib and etanercept data performed weaker compared to classifiers that were trained with data for each individual agent. Furthermore, biomarkers (such as proteins) chosen by the algorithms to be used within the models, as the ones more accurately predicting responsiveness, differed between tofacitinib and etanercept. Thus, it is crucial to develop unique models utilizing different variables for each biologic treatment.

Identifying peripheral relevant cell subsets using flow cytometry

The research of autoimmune diseases has been connected to experimental techniques involving flow cytometry and the consequent characterization of immune cell populations. Extending the frontiers of our understanding on responses to treatments in psoriatic disease can be achieved by advances in acquisition of data regarding immune cells. Machine learning techniques can be implemented in both stages of creating a predicting model, the first being biologic data acquisition and the second utilization of these data in conjunction with clinical parameters and creation of models. AI has reshaped the field of flow cytometry.

Flow cytometry has been widely used in immunology to describe intracellular and surface protein expression at the single-cell level. In brief, each cell is labelled with fluorescent-conjugated monoclonal antibodies and flows past lasers. The combination of light scatter characteristics and fluorescence parameters allows precise description of the nature of each cell. While technology has rap-

idly evolved since the 1960s, when flow cytometry was first used, these components remain largely unchanged [17]. However, data acquisition and analysis have significantly matured. Traditionally, a dot plot of two parameters enables gating of each cell population of interest. Complex multiparameter flow cytometry experiments have made the analysis of data extremely complicated. Attempts to phenotypically characterize rare cells of the periphery and associate them with disease-specific attributes have been limited so far by the cost of flow cytometry techniques and the complexity of manual analysis of datasets produced by state-of-the-art multidimensional (over 30 parameters) flow cytometers. Newer methods have been made available and have improved mining of data. AI has specifically been used in the context of flow cytometry to assist reduction of dimensionality, to identify cell populations, and to predict biologic outcomes such as response or no response for each sample using raw cytometry data [18].

High dimensional data produced by modern cutometers are difficult to interpret. Presentation of such data in two dimensions (graphs) enables proper subset investigation. Illustration of high dimensional data on such graphs demands heavy computational reformation. Dimensionality reduction has been facilitated utilizing a variety of models, including principal component analysis and UMAP [19].

MEDICAL PROFESSIONALS CAN HARNESS THE FULL POTENTIAL OF AI TO ENHANCE PATIENT CARE AS USHERING IN A FUTURE WHERE PERSONALIZED TREATMENT IS NOT JUST A POSSIBILITY, BUT A REALITY.

Automated algorithms have been created that can uncover sub-populations without any manual gating strategies. Unsupervised learning methods, such as hierarchical or K-means clustering can automatically gate cell sub-types. Computational pipelines, such as FLOCK, identify cell subsets without prior input of their estimated number [20]. Discovery of novel cell populations can be assisted by such techniques. However, supervised clustering models recognize known cell populations, as these have been annotated by humans. AI-assisted unsupervised techniques have already been used in the investigation of immune cells in patients with psoriatic disease. Specifically, patients and controls have been found to differ significantly in the fractions of 12 clusters of cells identified by AI, including Th17 and Th17.1 cells [21].

Machine learning models have been able to autonomously categorize each sample into distinct groups. For example, analyzing cytometry data, pipelines such as CITRUS can be used to classify samples for patients into biologic-responders and biologic-non-responders based on immunophenotype. Models using data at the single cell level are also available.

Exclusion of operator subjectivity, bias of gating, and undertaking of automated complex analyses may revolutionize the field and result in deeper understanding of peripheral cell subsets in psoriatic disease [22]. Many relevant cell populations may be recognized and associated with clinical parameters in the future.

UTILIZING IMMUNOPHENOTYPE PARAMETERS: FUTURE PERSPECTIVES

Advances in the field of flow cytometry and in the field of predictive model development are creating new perspectives. The use of immunophenotype data to assist predicting models is more relevant than ever. Indeed, fractions of blood cellular populations have been reported as potent biomarkers that predict the biologic-treatment responsiveness in rheumatic arthritis [23]. Acquiring data about cell populations in blood samples of patients and the treatment-mediated changes could be used to train AI models. Evidence suggests that specific cell populations in periphery significantly differ between patients and healthy controls and are affected by biologic therapy. To identify the precise cell populations that could eventually be utilized in machine learning approaches, we should first understand the complex associations between these populations and the immune-mediated disorder.

Identification of new cell subsets, characterization of the changes in their fractions in blood, and investigation of each subset's association with disease severity can ultimately be used to classify patients into groups with varying predictive responsiveness to a specific treatment. To develop such machine learning methods, studies determining the various peripheral cellular profiles for each disorder should be undertaken. Subsequent grouping based on the results of the blood tests could lead to individualized prescriptions of biologics and improved disease outcomes. For example, such an approach has been examined for a cohort of patients diagnosed with psoriatic arthritis using conventional techniques [24]. Specifically, researchers categorized patients by phenotypical cellular characteristics in four groups and treated them with a matching biologic agent accordingly. A strategically chosen allocation to treatment resulted in higher responsive rates compared to standard biological therapy.

However, proper categorization of patients and precise allocation to appropriate treatment requires understanding of the effect every therapeutical option exerts on each cell population and of whether that effect translates into meaningful improvement of relevant clinical outcomes. Some steps have been taken lately toward that direction. For example, anti-TNF agents have been reported to inhibit T helper (Th) 1, Th17, and Th22 cells, populations that produce pro-inflammatory cytokines implicated in many immune-mediated diseases including the psoriatic disease [25,26]. Adalimumab, an anti-TNFα monoclonal antibody, has also been shown to decrease circulating $CD3^-$ innate lymphoid cells that produce IL-17 and IL-22 [27]. Regarding anti-IL-17 agents, our research team has found that secukinumab or brodalumab treatment significantly inhibits Th17 and Th17.1 cells [28]. Furthermore, the biological effect of these monoclonal antibodies also concerns Tfh and Tph sub-populations (paper under consideration), which assist B cell reactions, antibody production, and the development of lymphoid-like structures within inflamed tissues where skewing of cells toward pro-inflammatory phenotypes occurs.

Using clustering methods to group patients with immunophenotype data may be a promising tool that will reveal which patients are more responsive to individualized, specific biologics. Such attempts have already been used in cancer research. Precise matching of patients with appropriate therapies may initiate a new era of medicine [29]. However, many challenges must be overcome. Incorrectly implemented AI methods providing poor recommendations may impact clinical treatment selections and worsen clinical outcomes.

ETHICAL CONSIDERATIONS

While the use of personalized data to create AI models could revolutionize medicine, ethical concerns, particularly regarding data privacy and potential biases, should be addressed. For example, data acquired from patients, including immunophenotypes, must be handled with confidentiality. Researchers and clinicians should ensure that patient data is anonymized and secure from unauthorized access or breaches. Adhering to regulations like the General Data Protection Regulation (GDPR) or the Health Insurance Portability and Accountability Act (HIPAA) is essential.

Furthermore, efforts to ensure fairness and prevent bias should be initiated. AI models can inadvertently perpetuate or amplify biases present in the training data. It is crucial that the data are representative of diverse populations to avoid biased predictions that could disadvantage certain groups. Regular audits and fairness assessments of the AI models are necessary.

Significantly, equity in access in AI-driven treatments should be ensured. Personalized medicine holds great promise but also risks widening healthcare disparities if it is only accessible to certain populations. Ensuring equitable access to treatments guided by immunophenotype data is an ethical imperative.

Concerns regarding transparency and accountability should also be addressed. There should be transparency in how AI models make predictions and how they are integrated into clinical decision-making. Healthcare providers should understand the limitations of these models and remain accountable for treatment decisions. While AI can provide valuable insights, it is crucial that it does not lead to an over-reliance that undermines the clinician's judgment. AI should be seen as a tool to aid, not replace, clinical expertise.

Last, patients should be involved in the decision-making process, especially when AI influences treatment options. The long-term effects of treatment decisions based on AI predictions should be monitored through continuous assessment and post-implementation surveillance.

Addressing these ethical considerations is fundamental to the responsible development and deployment of AI-driven personalized medicine. It ensures that the advancements in technology translate into equitable, safe, and ethical healthcare improvements.

CONCLUSIONS

The integration of AI and machine learning into the realm of immune-mediated disorders, including psoriatic diseases, heralds a new era of precision medicine. These advanced technologies promise to unravel the complex interplay between various blood cell subsets and the efficacy of biologic treatments. By identifying key immunophenotype parameters and pathologically significant cell subsets, AI can pave the way for novel biomarkers and therapeutic targets.

Furthermore, the use of machine learning models transcends mere identification. It holds the potential to transform disease diagnosis, streamline treatment selection, and personalize patient care. These advances could lead to more effective management of disorders and improved patient outcomes, as AI-driven insights fine-tune our understanding of disease pathophysiology and treatment response.

However, this technological advancement is not without its challenges. Ensuring equal access to data and ad-

vanced AI techniques is paramount to prevent widening the healthcare disparity gap. In addition, stringent measures must safeguard patient privacy and data security, as the ethical handling of sensitive health information is non-negotiable.

As we stand on the brink of this transformative juncture, it is imperative that the medical community, data scientists, and policymakers collaborate. This multidisciplinary approach is crucial to address the challenges head-on, establish robust ethical frameworks, and ensure that the benefits of AI in personalized medicine are accessible and equitable.

In essence, while AI holds the promise of revolutionizing the treatment of immune-mediated disorders, its successful and ethical implementation requires a concerted effort. By navigating these challenges, we can harness the full potential of AI to enhance patient care, ushering in a future where personalized treatment is not just a possibility, but a reality.

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