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GRAPPA 2024: Key Project Advances

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ABSTRACT. Significant progress toward several key initiatives was presented during the Project Key Advances session of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2024 annual meeting. Highlights included advancements from the Collaborative Research Network (CRN), with contributions from the Health Initiatives in Psoriasis and Psoriatic Arthritis Consortium European States (HIPPOCRATES) and developments in the complex-to-manage (C2M)/difficult-to-treat (D2T) psoriatic arthritis project. The presentation also included an update on the GRAPPA educational slide library. These activities underscore GRAPPA's continued dedication to fostering collaboration that advances psoriatic disease education and research toward improved patient outcomes.

Key Indexing Terms: education, GRAPPA, psoriasis, psoriatic arthritis, research

Introduction

The Group for Research and Assessment in Psoriasis and Psoriatic Arthritis (GRAPPA) has consistently demonstrated a strong commitment to advancing research and education in the field of psoriatic disease (PsD). Through the establishment of the GRAPPA Collaborative Research Network (CRN) and the research committee, we have seen significant improvements in patient care.[1] GRAPPA also prioritizes educational initiatives and has enhanced its international presence through sessions at major conferences and by offering online seminars that provide valuable educational resources for both patients and healthcare professionals.[2]

At the GRAPPA 2024 annual meeting, key advancements in pivotal projects were presented. Notably, the Health Initiatives in Psoriasis and Psoriatic Arthritis Consortium European States (HIPPOCRATES) shared progress in addressing critical challenges in PsD, including a prospective observational study identifying risk factors for psoriatic arthritis (PsA).[3] Another significant initiative was presented involving defining complex-to-manage (C2M)/difficult-to-treat (D2T) PsA, beginning with a comprehensive literature review, followed by an international survey of healthcare professionals.[4,5] The presentation also included updates from the GRAPPA educational slide library project.[6]

CRN updates

HIPPOCRATES update by Stephen Pennington, Denis O'Sullivan, and Oliver FitzGerald, on behalf of HIPPOCRATES

HIPPOCRATES is a large Innovative Medicines Initiative (IMI)-funded European consortium made up of 16 academic institutions, 5 pharmaceutical companies, 3 small-medium sized enterprises, and 2 patient representative organizations focused on improving early identification and patient outcomes in PsA.[3] The total budget is €22.5 million over a 5-year period that began in 2021 (Figure). HIPPOCRATES focuses on 4 specific areas of unmet need: (1) the development of a diagnostic test and/or algorithm for PsA (work package 1 [WP1]); (2) the identification of risk factors to determine which patients with cutaneous psoriasis (PsO) will develop PsA (WP2); (3) improving understanding of the clinical and/or molecular factors contributing to joint damage in PsA (WP3); and (4) the development of a precision medicine–informed treatment approach for PsD (WP4).

A significant development in the third year of the project has been the signing of a consortium-wide data sharing agreement facilitating the upload of clinical and molecular data to a secure HIPPOCRATES data management platform (SHDMP). To date, data from > 2000 patients with PsA have been uploaded for machine learning (ML)/artificial intelligence (AI) analysis that is now underway.

In WP1, progress has been made on the identification of clinical and molecular markers differentiating PsA from cutaneous PsO. Analysis of various imaging techniques useful in early detection of PsA is underway, with a paper on fluorescence optical imaging in preparation. Tissue mapping using 52 antibodies for multiplex immunohistochemistry has also been established. This antibody panel will be used to compare synovial tissue from PsA

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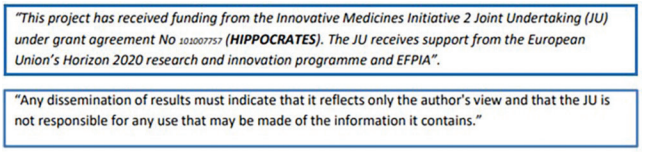

Figure. Administrative structure and agreements for the HIPPOCRATES Prospective Observational Study. Retrieved from https://www.hippocrates-imi.eu/about/funding. EFPIA: European Federation of Pharmaceutical Industries and Associations; HIPPOCRATES: Health Initiatives in Psoriasis and Psoriatic Arthritis Consortium European States; JU: joint undertaking.

with that of rheumatoid arthritis (RA) and to compare the skin of patients with PsO with and without PsA.

In WP2, results from a pilot study that analyzed prospectively collected serum of 90 patients and looked for multiomic markers to identify patients at risk of developing PsA has been completed. These omic platforms include genomics (both targeted—Olink and multiple reaction monitoring—and unbiased), proteomics, metabolomics, and lipidomics. Data are now being subjected to combined ML/AI analysis. The HIPPOCRATES Prospective Observational Study (HPOS), an online study aiming to recruit and follow 25,000 people with cutaneous PsO, has launched in 4 countries with > 3000 people registered to date. Organizers are planning launches in up to 11 additional countries by the end of 2024.[3]

In WP3, which includes a 10-year postdated retrospective study of PsA damage progression, investigators used high-resolution peripheral quantitative computed tomography to quantify microstructural bone damage in the metacarpophalangeal joints. Most patients developed microstructural damage within 3 years from presentation, driven mainly by higher disease activity as measured by the Disease Activity Score in 28 joints based on C-reactive protein (DAS28-CRP). Investigators found that microstructural bone deterioration can be slowed by treatment with biologic disease-modifying antirheumatic drug (bDMARD) therapy initiated within a 3-year window of opportunity.

Finally, in WP4, investigators have identified candidate epigenetic (chromatin confirmation) markers that predict response to adalimumab and tofacitinib treatment. Validation studies in large independent cohorts are being planned. Additional studies looking for multiomic markers of response to treatment with methotrexate, adalimumab, and tofacitinib are also underway.

Over the final 2 years of HIPPOCRATES, we expect to design algorithms for early diagnosis of PsA and identifying risk of PsA development in patients with cutaneous PsO. We expect to identify patients with PsA at risk of radiographic damage progression and develop candidate biomarkers of baseline predictors of response to treatment (adalimumab, methotrexate, tofacitinib). We are also looking for additional funding opportunities to further the important work of HIPPOCRATES, including validation studies, HPOS follow-up, the SHDMP, and continuing to build a catalog of research samples. Collaboration with other large consortia, such as the Accelerating Medicines Partnership–Autoimmune and Immune-Mediated Diseases (AMP-AIM) program, Elucidating the Landscape of Immunoendotypes in Psoriatic Skin and Synovium (ELLIPSS), will be an important component of future studies, in particular where validation of findings from one consortium can be undertaken in the other.

Update on the GRAPPA research project toward developing a definition of C2M/D2T PsA by Fabian Proft, Christine Lindsay, Philip Mease

The ongoing effort to define C2M/D2T PsA represents a crucial step in addressing unmet needs for patients with persistent, refractory disease. The GRAPPA research project aims to establish a universally accepted definition of D2T PsA, leveraging real-world evidence and healthcare provider insights to guide clinical practice, pharmaceutical research, and regulatory approval pathways. The necessity of this definition arises from the growing identification of patients who continue to experience disease activity despite multiple lines of treatment, indicating a need for more targeted therapeutic strategies.

- *Why do we need C2M/D2T criteria for PsA?* The reasons for treatment failure in patients with PsA are multifactorial, necessitating a comprehensive analysis of these factors to enhance patient care. Recently, the classification of these factors into 2 broad groups has gained attention: a larger group that encompasses all possible reasons for treatment failures, including those not directly related to ongoing inflammation, termed C2M, and a more specific group focusing only on situations where there is a true biological nonresponse to advanced treatments, as indicated by persistent active inflammatory processes, termed D2T or treatment-refractory (TR) PsA. Developing a standardized definition of D2T PsA is vital for several reasons. First, it provides guidance to clinicians who encounter patients with TR PsA as defined by ongoing active disease despite the use of multiple therapies including advanced treatments like bDMARDs and targeted synthetic DMARDs (tsDMARDs). These patients, often described as having "tried everything," require a structured framework for evaluation and management, offering clinicians a path forward when traditional treatments fail. Recent real-world evidence suggests that 10% to 30% of patients with PsA may fall into the D2T category, highlighting the high clinical relevance of this population.[7,8] Additionally, defining D2T PsA will assist pharmaceutical companies in clinical trial design targeting this refractory population, particularly through dual therapy and therapy intensification studies. A clear D2T definition will enable the selection of appropriate study populations, ensuring that trials address the specific needs of these patients. For regulatory agencies, this definition supports the case for innovative therapeutic strategies, even if associated with higher risks of adverse events, as the benefit of controlling persistent disease in these patients may outweigh the potential risks.

Finally, educating payors about the necessity of dual therapy or intensified dosing for D2T PsA is critical to ensuring access to care. Without a standardized definition of D2T, it can be challenging to justify the additional cost and complexity of

these treatments, despite their potential to significantly improve outcomes in patients who have exhausted conventional treatment options.

• *Learning from other D2T initiatives.* The concept of D2T has been explored in other rheumatic diseases, most notably in RA and axial spondyloarthritis (axSpA). The European Alliance of Associations for Rheumatology (EULAR) definition of D2T RA serves as a benchmark for developing similar criteria in PsA.[9] This definition, based on a structured approach, incorporates patient-reported outcomes, objective signs of inflammation, and treatment history. Similarly, the Assessment of SpondyloArthritis international Society (ASAS) task force definition of D2T axSpA offers further insights into how refractory disease can be identified and managed.[10] These initiatives provide a framework for the GRAPPA research project to build upon, ensuring that the definition of D2T PsA is both comprehensive and clinically relevant.

• *Progress of the GRAPPA project on C2M/D2T PsA.* During the last year, the GRAPPA research project has made significant progress in defining D2T PsA, beginning with a scoping literature review.[4] By highlighting the substantial heterogeneity in the definition of D2T PsA in the literature, this review emphasized the need for a universally accepted definition. "Difficult-to-treat" was the most frequently used term followed by "refractory PsA." The project has considered the nomenclature carefully, recognizing the need for consistent terminology that resonates with both clinicians and regulatory agencies. The results of this review underscore the complexity in developing a standardized definition, as the criteria must balance clarity with clinical relevance while being as specific as possible.

To further inform the development of D2T PsA criteria, GRAPPA conducted an international survey of healthcare professionals.[5] The survey found that 82.5% of respondents supported differentiating between C2M and D2T PsA, suggesting that distinct categories may be needed to address varying levels of disease complexity. Around 90.5% of respondents agreed that the inclusion of objective signs of ongoing inflammation was essential to the definition of D2T PsA. Specific measures, such as persistently elevated acute-phase reactants (eg, erythrocyte sedimentation rate or CRP), were favored by nearly half of the respondents, and 69.5% advocated for including imaging assessments. Additionally, there was strong support (78%) for counting the number of different advanced therapies used and accounting for different modes of action (MOA). When it came to defining the threshold for D2T PsA, 41% of respondents agreed that a patient should have failed at least 1 conventional synthetic DMARD and 2 b/tsDMARDs with different MOAs. This feedback has provided valuable insights into how the definition could be structured, ensuring it reflects the real-world challenges faced by clinicians.

According to current consensus, D2T PsA is defined as "truly treatment-refractory disease," marked by objective signs of active disease despite appropriate interventions, whereas C2M represents a broader concept that includes a wider range of reasons for treatment failures. The next step in the GRAPPA project is to initiate a Delphi process, aimed at building consensus within the working group to refine and finalize the definitions for both C2M and D2T PsA. Following this, a formal vote on the proposed definition will be conducted among GRAPPA members, with the goal of establishing a definitive consensus by 2025.

Once these definitions are finalized, they will become essential tools for clinicians, researchers, and regulators, providing clear guidance on identifying and managing patients with C2M and D2T PsA. By addressing the needs of this underserved population, the GRAPPA project aims to improve outcomes for patients with refractory disease.

GRAPPA slide library update by Gizem Ayan, Fabian Proft, and Philip Helliwell

The GRAPPA slide library update project, launched in March 2022, was supported by the GRAPPA education committee and a dedicated team of experts, led by Philip Helliwell, Fabian Proft, and Gizem Ayan, in order to update the original library created in 2013. Annie Spangler, who succeeded Janine Kowack after her retirement, provided administrative support.[11] The project used a new technical platform originally developed as part of the ASAS slide library.[12] This comprehensive effort concluded in June 2023 and the updated GRAPPA slide library was unveiled at the annual trainee symposium in July 2023.

Over the past year, the slide library team has worked on several further updates and improvements. First, an analytics program has been implemented in the library to better understand user preferences. To guide future improvements, this program provides data on which slides are most frequently downloaded and from which geographical locations the slides are most frequently used. A second step was initiated to revise the slides according to reader feedback. Eight slides have been revised according to the reader feedback to ensure higher quality and accuracy. The third step will be embarking on a translation initiative. After the GRAPPA 2023 annual meeting, a project was initiated to translate the slide library into 6 pilot languages (Brazilian Portuguese, German, Italian, Japanese, Spanish, and Turkish). The aim of this project is to increase the visibility and educational impact of the slide library. Availability in multiple languages will facilitate its use in lectures and presentations worldwide. The translation process began with the identification of a coordinator for each language in January 2024. Each coordinator then put together a team of people interested in PsD, consisting of a leader and translators who were native speakers of each individual language. The teams included at least 1 rheumatologist and 1 dermatologist. Final translated versions were reviewed and approved by the coordinators. At the GRAPPA 2024 annual meeting and trainee symposium, 5 of the 6 languages were launched (Brazilian Portuguese, Italian, Japanese, Spanish, and Turkish); these can be accessed at https://slides.grappanetwork.org.[6] All contributors were provided with certificates upon completion by the GRAPPA education committee in recognition of their hard work and dedication to this project. Future translations are planned, starting with French and Arabic; analytics results will guide decisions on candidate language selections going forward.

Moreover, the slide library will continue to be regularly updated, facilitated by building upon slides from presenters at upcoming meetings. During the coming months, the treatment slides will be revised, and translations will be subsequently implemented. The next steps involve planning regular updates to establish a dynamic, continuously evolving library.

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ETHICS AND PATIENT CONSENT

Institutional review board approval and patient consent were not required.

PEER REVIEW

As part of the supplement series GRAPPA 2024, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

REFERENCES

1. Stober C, McInnes IB, Raychaudhuri S, et al. Proceedings of the. GRAPPA-Collaborative Research Network (CRN) meeting. J Rheumatol 2022;49(6 Suppl 1):57-63.
2. Ng BCK, Jadon D, Adebajo A, et al. Proceedings of the GRAPPA 2022 Executive retreat. J Rheumatol 2023;50(Suppl 2):71-7.
3. HPOS Study. The Hippocrates Prospective Observational Study (HPOS). [Internet. Accessed April 9, 2025.] Available from: https://hpos.study
4. Singla S, Ribeiro A, Torgutalp M, Mease PJ, Proft F. Difficult-to-treat psoriatic arthritis (D2T PsA): a scoping literature review informing a GRAPPA research project. RMD Open 2024;10:e003809.
5. Ribeiro AL, Singla S, Chandran V, et al. Deciphering difficult-to-treat psoriatic arthritis (D2T-PsA): a GRAPPA perspective from an international survey of healthcare professionals. Rheumatol Adv Pract 2024;8:rkae074.
6. GRAPPA. GRAPPA Slide Library. [Internet. Accessed April 9, 2025.] Available from: https://slides.grappanetwork.org
7. Alp G, Kara M, Cinakli H. Potential difficult-to-treat psoriatic arthritis real-world prevalence and contributing factors. Clin Exp Rheumatol 2025;43:41-7.
8. Philippoteaux C, Marty-Ane A, Cailliau E, et al. Characteristics of difficult-to-treat psoriatic arthritis: a comparative analysis. Semin Arthritis Rheum 2023;63:152275.
9. Nagy G, Roodenrijs NMT, Welsing PM, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis 2021; 80:31-5.
10. Poddubnyy D, Baraliakos X, Navarro-Compán V, Torgutalp M, van der Heijde D; the ASAS Difficult-to-Manage Axial Spondyloarthritis Task Force. The Assessment of Spondyloarthritis International Society (ASAS) definition of difficult-to-manage axial spondyloarthritis [abstract]. Arthritis Rheumatol 2024;76(Suppl 9).
11. Ayan G, Aydin SZ, Coates LC, et al. GRAPPA 2023: major projects, key advances, and milestones. J Rheumatol 2024;51(Suppl 2):65-9.
12. Assessment of SpondyloArthritis international Society. ASAS Slide Library. [Internet. Accessed April 9, 2025.] Available from: https://www.asas-group.org/education/asas-slide-library/