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European Network on Optimizing Treatment With Therapeutic Antibodies in Chronic Inflammatory Diseases: Overview, Progress and Perspectives

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ABSTRACT

Treatment of chronic inflammatory diseases has been revolutionized with the introduction of targeted therapies using therapeutic antibodies. However, a large proportion of patients do not respond to treatment, or they lose response over time. To overcome this challenge, researchers have started to investigate strategies for treatment optimization, based on the development of patient stratification tools and therapeutic drug monitoring (TDM). The aim of the COST Action European Network on Optimizing Treatment with Therapeutic Antibodies in chronic inflammatory diseases (ENOTTA) is to create an interdisciplinary, pan-European network to defragment and structure scientific research in this field. Through the network, ENOTTA will facilitate the implementation of tools for patient stratification, as well as individualized (TDM-guided) approaches. These strategies should be cost-effective and provide therapeutic antibody treatment optimization for the treatment of chronic inflammatory diseases. This article highlights the key achievements of the ENOTTA consortium to date.

1 | Introduction

Chronic inflammatory diseases, including rheumatoid arthritis, Crohn's disease, and psoriasis, can affect people of all ages and represent a major challenge for healthcare systems and a significant impact on patients' quality of life. However, the age distribution is quite different according to the disease (20 years for IBD [1], 30–69 years for Rheumatoid arthritis (RA), and under

The first two authors contributed equally to this article.

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the age of 69 for psoriasis). The disease onset can be early in life, and with no cure available, many patients require lifelong treatment that necessitates the use of safe, tolerable, and effective drugs. Treatment of chronic inflammatory diseases has been transformed with the introduction of therapeutic antibodies (e.g., infliximab, adalimumab, etanercept, and rituximab). The use of these drugs is aimed at long-term control of inflammation, regardless of the site (e.g., joints, skin, or gastrointestinal tract) [2].

However, in many cases, patients do not fully respond to treatment, experience a partial response, or lose response over time. Failure to achieve complete remission may be due to suboptimal dosing or immunogenicity leading to the development of anti-drug antibodies (ADA) [3]. Therapeutic antibodies exhibit significant interpatient variability in pharmacokinetic characteristics, leading to differences in exposure and thus clinical responses [4]. The emergence of ADA results in different clinical consequences, ranging from mild infusion/injection site reactions to anaphylaxis and a lack of therapeutic effect [5]. Subtherapeutic serum drug concentration might also be caused by individual differences in drug bioavailability [6], due to non-modifiable factors, such as age in canakinumab and biological sex [7].

In the last two decades, a number of centers across Europe and beyond have investigated the concept of therapeutic drug monitoring (TDM) in the setting of chronic inflammatory diseases treated with therapeutic antibodies. The most frequently analyzed monoclonal antibodies in chronic inflammatory diseases were infliximab and adalimumab, primarily for clinical use in gastroenterology and rheumatology [8, 9]. However, model-informed precision dosing (MIPD), the application of pharmacometrics models to optimize drug dosing, is applied in only a small number of clinical studies [10]. Optimizing treatment by adjusting the dose of a therapeutic antibody based on serum drug and ADA concentrations to achieve a drug exposure associated with the highest possible response rate has multiple potential advantages over adjusting treatment based on clinical outcomes alone. Transferring knowledge and techniques to other centers remains challenging, as in-house expertise is often needed to interpret and translate TDM data effectively for patient benefit. While more MIPD companies and specialized TDM laboratories are now offering services across multiple hospitals, the broader issue lies in moving beyond implementation to ensure that sufficient research and evidence generation underpin clinical practice. In addition, each hospital/research center uses its own TDM protocols and assays, and the lack of harmonization leads to a significant duplication of effort and difficulties in comparing results between centers, contributing to insufficient evidence and the absence of clear, universally accepted guidelines. Despite efforts to bring together clinicians and pharmacometricians, initiatives for the TDM of therapeutic antibodies remain too isolated [11].

To improve patient care in the field of therapeutic antibodies, several challenges need to be addressed [6]. First, stratification of patients before treatment ("Which therapeutic antibody to use for a given patient") is becoming increasingly important because some patients do not respond to certain therapeutic antibodies. However, no such stratification signature has yet been identified that has been successfully translated to the clinic, and further research is urgently needed. In contrast, some patients have received supra-optimal doses, resulting in overexposure with poor outcomes in some cases (primary non-responders), while other patients achieve remission while being unnecessarily overexposed [12]. The potential and clinical application of biomarkers of response face other important challenges, such as sensitivity, reproducibility, and complexity of multi-biomarker panels [12]. So, there is a pressing need for a clear consensus about the most promising and fit-for-purpose biomarkers of therapeutic antibody response.

TDM, i.e., "the use of drug concentrations to optimize the dose for an individual patient", is a clinical decision-making tool based on blood/serum drug and ADA concentrations that aims to improve treatment efficacy by providing individual guidance for more accurate use and dosing of therapeutic antibodies ("the right dose for the right patient at the right time") [13]. To effectively implement this evidence-based optimization, clinicians, patients, and other stakeholders need to be educated and informed about its potential benefits, although more evidence is needed to fully support its widespread use. So far, there are a lot of consensus guidelines that have been published in the field of inflammatory bowel disease [14] and some points to consider have been developed by the European Alliance of Associations for Rheumatology (EULAR) task force for inflammatory rheumatic and musculoskeletal diseases [15, 16]. Although TDM may help patients with IBD, inflammatory arthritis, or psoriasis to maintain the clinical outcomes, the definitive evidence on efficacy and cost-effectiveness is still lacking [17].

It is also important to note that therapeutic antibodies generate considerable costs in many European countries. In France,e.g., the amount spent by health insurance was €1.5 billion for the three main prescribing specialties (rheumatology, gastroenterology, and dermatology). The annual expenditure for patients with rheumatoid arthritis receiving therapeutic antibodies is estimated to be three times higher than for patients who do not receive such treatment [18]. Treatment with therapeutic antibodies is expensive and results in significant personal, societal, and healthcare costs, e.g., for anti-TNF in European Countries [19]. The expanding therapeutic armamentarium holds great potential for improving patient care. However, treatment is often based on "trial-and-error-medicine" with the risk of suboptimal care at a higher cost. The few studies available, mainly based on modeling or retrospective studies of originator drugs rather than the cheaper biosimilars, showed a significant cost per quality-adjusted life year (QALY) gain [20]. However, comparative prospective cost-effectiveness studies are still lacking. Most of the studies published to date support the interest of TDM in cases of loss of response (reactive TDM) [21].

The European Cooperation in Science and Technology (COST) Association supports, on average, 60 'Actions' that consist of networks. An Action is an interdisciplinary research network that brings researchers and innovators together to investigate a topic of their choice for 4 years (https://www.cost.eu/). In 2021, the COST Association awarded the "European Network on Optimising Treatment with Therapeutic Antibodies in chronic inflammatory diseases" (ENOTTA).

The aim of ENOTTA is to establish an interdisciplinary, pan-European network to defragment and structure scientific

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research in the field of therapeutic antibodies and to facilitate the implementation of individualized (TDM-guided) cost-effective dose optimization of these drugs in daily clinical practice for the treatment of chronic inflammatory diseases. This article highlights the key objectives and progress to date made by the COST Action ENOTTA.

1.1 | Mission of the ENOTTA Network

The primary goal of the ENOTTA network is to transform current practice by enabling patient stratification at the start of treatment, ensuring the right drug is allocated to the right patient. This goal is pursued through a transdisciplinary approach that integrates expertise across different IMIDs and brings together clinicians, bioanalysts, clinical pharmacologists, pharmacometricians, and health economists. Additional information and resources on this topic can be found on the official website (https://enotta.eu/), which provides comprehensive updates.

ENOTTA aims to optimize therapeutic antibody use in chronic inflammatory diseases through TDM-guided, patient-tailored dosing, standardization of protocols, interdisciplinary collaboration, and capacity building to translate research into cost-effective clinical practice across Europe. As each hospital/research center uses its own TDM methodologies, protocols, and assays, there is a strong need for an effective, harmonized approach to optimize TDM assays. Working towards universal standards and laboratory practices for the different assays will significantly improve the quality and reproducibility of prospective multicenter clinical trials.

Significant innovation is expected from computational population pharmacokinetic-pharmacodynamic models that predict treatment response and allow dose optimization. The concept of MIPD was first introduced over five decades ago by pioneers Lewis Sheiner [22] and Roger Jelliffe [23], although the term 'MIPD' emerged much later in the mid-2010s and keeps gaining interest in the scientific community [24]. Several other terms have emerged, such as "concentration-guided dosing", gathering both therapeutic window and target concentration approaches [25].

Developing guidelines for clinical management and best practices for individualized (TDM-guided) dose optimization is a key focus of ENOTTA through the development of a pan-European community, with its effectiveness assessed through a multidimensional health technology assessment approach that evaluates clinical outcomes, patient-reported outcomes, cost-effectiveness, and broader societal impact. Data on the cost-effectiveness and acceptability of TDM of biopharmaceuticals in chronic inflammatory diseases are lacking. There is a need to investigate how TDM can reduce the cost of therapeutic antibodies per QALY below the willingness to pay. There is a scarcity of data regarding the acceptability of TDM of biopharmaceuticals. Shared decision-making between the physician and the patient is considered essential by European societies, but has not yet been well studied so far.

ENOTTA is establishing a network of TDM centers across Europe, which represents a critical first step towards the widespread implementation of therapeutic antibody optimization in clinical practice by enabling expertise sharing, protocolharmonization, and generation of reproducible multicenter data. This initiative is developed in close collaboration with epidemiologists, computer scientists, health economists, pharmacists, and health authorities, ensuring that TDM will be accessible to the entire European population. These advancements are essential for the implementation of TDM-based dose optimization of therapeutic antibodies, ultimately leading to improved patient care and reduced burden on the healthcare system. Some of the key objectives of ENOTTA are presented in Table 1.

1.2 | Organization and Working Groups

In its organizational structure, ENOTTA comprises five working groups (WG) devoted to the achievement of its objectives (Figure 1).

Working group 1 (WG1) is focused on optimizing patient stratification strategies for patients at the start of treatment ("which therapeutic antibody to use for a particular patient"). WG1 initiated a structured overview of the patient biobank among hospitals and research centers, which may serve as a valuable resource for future collaborative studies. Additionally, this group is also investigating patient-specific factors and clinical covariates that influence treatment response, which help determine the optimal starting dose for maximum efficacy. Finally, WG1 is intended to develop guidelines to improve patient stratification at treatment onset, ensuring that each patient receives the appropriate drug at the correct dose for the best possible outcome.

WG2 is primarily dedicated to training on MIPD, as demonstrated by its Webinar series and the 2025 Training School at KU Leuven. STSMs and joint research efforts within WG2 illustrate how ENOTTA promotes collaboration among academic centers across Europe.

WG3 is investigating the current practice and necessary actions for harmonizing and standardizing TDM assays to enable meaningful comparison of results across different hospitals/research centers.

WG4 is focusing on cost-effectiveness assessment and implementation of TDM of therapeutic antibodies in inflammatory diseases. In addition, the WG4 addresses the aspect of acceptability and affordability of TDM by both patients and caregivers.

Lastly, WG5 is working on dissemination and sustainability by focusing on the coordination of all communication and dissemination activities of the COST Action ENOTTA through the website, social media, open access journals, and other channels in close collaboration with the Science Communication Coordinator. In addition, WG5 is responsible for training and organizing educational activities, such as training schools and webinar series within the Action (https://enotta.eu/). Education on TDM is scattered across European countries and disciplines [26]. WG5 contributes to educating clinicians, pharmacists, and health professionals on TDM of biopharmaceuticals.

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TABLE 1 | Objectives of the ENOTTA COST action.

Type of objective	Content
Research coordination objectives	Create an interdisciplinary society of researchers, clinicians, experts, and stakeholders working on dose optimization of therapeutic antibodies by organizing interdisciplinary meetings and setting up new collaborations.
	Investigate and develop patient stratification tools to predict and optimize treatment choice at initiation, with the contribution of predictive analytics companies or academic groups.
	Develop guidelines for clinical management and best practices for individualized (TDM-guided) dose optimization.
	Improve the reproducibility, standardization, and harmonization of TDM assays and protocols by creating a pan-European TDM community to share best laboratory practice.
	Set up a comprehensive and structured overview of the availability of patient data/samples to facilitate future pan-European collaborations.
	Evaluate the cost-effectiveness of individualized (TDM-guided) dose optimization of therapeutic antibodies as an instrument to reduce healthcare expenditures, thus ensuring access and affordability.
	Investigate how TDM may be implemented and secured in the community with the support of e-Health SMEs.
Capacity-building Objectives	Facilitate scientific collaboration and knowledge exchange by organizing and coordinating an open, sustainable, and multidisciplinary network using an electronic platform.
	Stimulate the development of a joint research agenda, post-marketing studies, and prospective multicenter clinical trials.
	Offer a balanced vision and expertise to European and national decision-makers and stakeholders through their participation in the network.
	Form an educational programme by organizing training schools, webinar series, and short-term scientific missions (STSMs) to offer training in areas such as antibody production, pharmacometrics of therapeutic antibodies, data sharing and data storage, tertiary clinical centers, and clinical trial design.
	Help Young Researcher Investigators (YRIs) and researchers to develop and expand their professional networks, meet experts and stakeholders, and create opportunities for collaborations.
	Provide the opportunity to SMEs and pharmaceutical companies to join the Action (pharmacometricians, biostatisticians, assay developers, software producers, data managers, and clinical trial designers) and create an international platform, gathering both clinical and biological resources.

1.3 | Outreach Activities

The COST Action ENOTTA is working to provide a framework to network, maintain, and expand a collaboration among all potential stakeholders across Europe, including academic institutions, hospitals, scientific European societies, patient organizations, and health ministries. Such a structure will facilitate the sharing and exchange of know-how, promote the dissemination of knowledge, and thus act as a catalyst in personalized medicine and its application in Europe and worldwide.

The COST Action ENOTTA aligns with the current EULAR guidelines, which identify TDM and its cost-effectiveness as a societal goal [27].

Achieving ENOTTA's goals requires the development of competencies among a diverse group of professionals, including biopharmaceutical and biomedical researchers, assay developers, and clinicians from various fields, such as rheumatic diseases, inflammatory bowel disease, psoriasis, neuroinflammatory diseases, and pediatric chronic inflammatory diseases. ENOTTA members both contribute to and benefit from the sharing and integration of knowledge, insights, and scientific discussions. Key international societies, such as the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) or the European Association for Clinical Pharmacology and Therapeutics (EACPT), will be involved in scientific discussions on the implementation of personalized medicine. Pharmaco-economists involved in ENOTTA are assessing the efficiency of TDM compared to usual care.

Furthermore, the (long-term) end-users who will benefit from the network are clinicians and patients (represented by patient organizations and Patient Partners) as the network paves the way towards TDM improving treatment outcomes.

The involvement of national and international policymakers, healthcare, commercial organizations, and research funders in the discussions is important for the reimbursement of TDM. In

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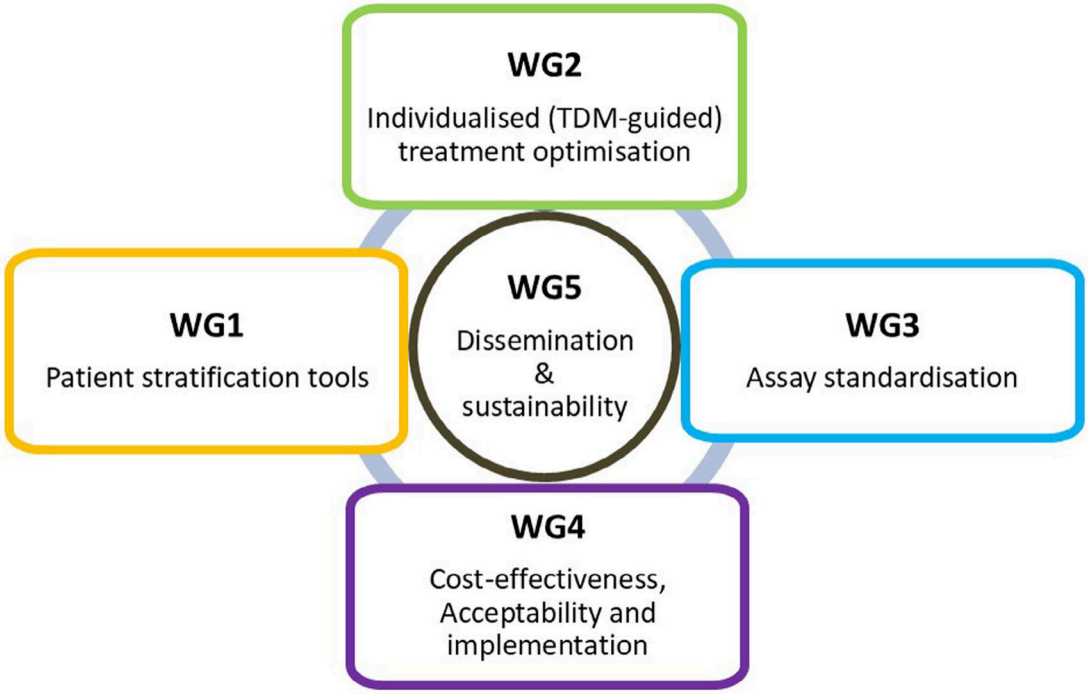

FIGURE 1 | Working groups of ENOTTA COST action.

addition, the results of the research activities embedded in the inflammatory diseases area will be used as a basis for extending the treatment optimization of therapeutic antibodies to other diseases, such as cancer, metabolic, cardiovascular, or infectious diseases.

The results of the COST Action ENOTTA could be used, by *in silico* simulation approaches, to facilitate the design of European prospective randomized multicenter clinical trials to investigate whether patient stratification and individualized (TDM-guided) dose optimization is clinically and/or cost-effectively superior to usual care.

1.4 | Progress and Impact

ENOTTA brings together five working groups (WGs) addressing complementary aspects of therapeutic antibody optimization in immune-mediated inflammatory diseases (IMIDs).

WG1 develops and curates a biobank of patients treated with therapeutic antibodies, available through the ENOTTA website. It also conducts a systematic review of biomarkers linked to anti-TNF-α response and has launched a Delphi panel to establish consensus on biomarker-driven patient stratification.

WG2 advances individualized treatment optimization by applying pharmacokinetic–pharmacodynamic models and algorithms for therapeutic drug monitoring (TDM) guided dosing in chronic inflammatory diseases.

WG3 promotes assay standardization and coordinates a pan-European network of 63 TDM hospitals and research centers, enabling future collaborative clinical trials and harmonization of analytical methods. Information on available proficiency testing schemes is also provided to support external quality assessment.

WG4 investigates clinical integration of TDM through Europe-wide surveys on current practices, stakeholder roles, barriers to implementation, and educational needs. Additional initiatives include cost-effectiveness analyses, educational strategies, and webinars addressing pharmacoeconomics and personalized medicine.

WG5 ensures dissemination, communication, and sustainability of ENOTTA through its central website, scientific meetings, training activities, and outreach via social media and professional networks. Some collaborations in the direction of the pharmaceutical industry, health authorities, patients' associations, and payors have been established during meetings and webinars, as illustrated on our website (https://enotta.eu/).

These coordinated efforts foster scientific collaboration, harmonization of practices, and translation of TDM-guided strategies into routine clinical care, ultimately aiming to improve patient outcomes across Europe.

2 | Conclusion

As a first-of-its-kind, the COST Action ENOTTA is an interdisciplinary, pan-European network aiming to facilitate the implementation of patient stratification tools, as well as individualized (TDM-guided), cost-effective dose optimization of therapeutic antibodies in daily clinical practice for the treatment of chronic inflammatory diseases. The activities are expected to benefit not only clinicians but also researchers and patients living with chronic inflammatory diseases, treated with therapeutic antibodies.

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TABLE 2 | Core group members of ENOTTA COST action.

Nr.	Country	Core group members
1.	Cyprus (CY)	Olga Pitsillidou
2.	Sweden (SE)	Elisabet Nielsen
3.	France (FR)	Denis Mulleman
4.	Serbia (RS)	Nataša Bogavac-Stanojević
5.	Belgium (BE)	Erwin Dreesen
6.	Bulgaria (BG)	Guenka Petrova
7.	Türkiye (TR)	Mehmet Itik
8.	Serbia (RS)	Azra Guzonjić
9.	Bulgaria (BG)	Konstantin Tachkov
10.	Hungary (HU)	Zsombor Zrubka
11.	France (FR)	Athan Baillet
12.	Netherlands (NL)	Floris Loeff
13.	Norway (NO)	Silje Skrede
14.	Cyprus (CY)	Aliki Peletidi
15.	Serbia (RS)	Jelena Munjas
16.	Portugal (PT)	Marlene Santos
17.	Türkiye (TR)	Güldal İnal Gültekin
18.	Iceland (IS)	Georgios Kararigas
19.	United Kingdom (UK)	James Bluett
20.	Poland (PL)	Paweł Kawalec
21.	France (FR)	Blandine Hesnault

2.1 | ENOTTA Collaborators

ENOTTA's collaborative network includes 21 core group members across 16 countries, as outlined in Table 2.

The Management Committee (MC) of ENOTTA is composed of 35 members from 23 countries (Albania, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Denmark, Estonia, France, Greece, Hungary, Iceland, Italy, North Macedonia, Norway, Poland, Portugal, Romania, Serbia, Spain, Sweden, Türkiye, and the United Kingdom). Of these, 14 countries are ITCs (Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Estonia, Greece, Hungary, North Macedonia, Poland, Portugal, Romania, Serbia, and Türkiye). The MC demonstrates balanced gender representation, with 21 female (60%) and 14 male (40%) members.

The Working Groups currently count 280 members representing 36 countries, including 2 Near Neighbor Countries (NNC) and 2 non-COST member countries. Among them, a large proportion come from ITCs (203 members), and nearly half are Young Researchers and Innovators (YRI, $n = 145$). In terms of gender distribution, the groups include 168 women and 112 men, highlighting a favorable balance towards female representation.

Author Contributions

J.B. – investigation, manuscript reviewing and editing, manuscript approval. N.B.-S. – investigation, manuscript reviewing and editing, manuscript approval. E.D. – investigation, manuscript reviewing and editing, manuscript approval. M.I. – investigation, manuscript reviewing, and editing, manuscript approval. G.K. – investigation, manuscript reviewing and editing, manuscript approval. P.K. – investigation, manuscript reviewing and editing, manuscript approval. D.M. – design of the paper, concept paper, project writing, manuscript writing, manuscript approval, and corresponding author. G.P. – design of the paper, concept paper, project writing, manuscript writing, manuscript approval. M.R. – investigation, manuscript reviewing and editing, manuscript approval, and corresponding author. M.S. – investigation, manuscript reviewing and editing, manuscript approval. S.S. – investigation, manuscript reviewing and editing, manuscript approval. K.T. – concept paper, study design, study performance, manuscript writing, manuscript approval.

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Conflicts of Interest

J.B. reports a research grant award from Pfizer and travel/conference fees in the last 3years from Fresenius Kabi and Novartis. E.D. received consultancy fees from Alimentiv, lecture fees from Celltrion and Galapagos, and financial support from Celltrion, Pfizer, Prometheus Biosciences, R-Biopharm, and Sandoz outside the submitted work, with all honoraria/fees being paid to KU Leuven and not to any personal account of E.D. D.M. reports travel/conference fees from Celltrion Healthcare to attend the French Society for Rheumatology in 2022. All other authors declared no competing interests for this work.

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