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Maximilian Weber

Department of Immunology
and Rheumatology, Charité –
Universitätsmedizin Berlin,
Berlin, Germany

Katharina Schneider

Institute for Molecular
Medicine, Ludwig Maximilian
University of Munich, Munich,
Germany

Exploring the role of biochemical Signaling in autoimmune diseases

Maximilian Weber and Katharina Schneider

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Abstract

Why does the immune system sometimes turn against the body it's supposed to protect? We've been asking this question for years, and frankly, the answers keep getting more complicated the deeper we look. This study set out to examine—or rather, to map out—the tangled web of biochemical signals that seem to drive autoimmune pathology. We looked at five conditions: rheumatoid arthritis, multiple sclerosis, type 1 diabetes, lupus, and psoriasis. The patient cohort was fairly large; 847 individuals recruited from four German university hospitals between 2019 and 2023. Blood samples were collected and we ran cytokine panels alongside pathway activation assays. What we found was, in some ways, predictable but also surprising in places. TNF- α varied quite a bit across conditions. Lupus patients had the highest levels at 223.7 pg/mL while type 1 diabetes showed only 98.6 pg/mL. IL-6 followed a similar pattern, more or less. The Th17 pathway was particularly active in psoriasis (IL-17 hitting 267.3 pg/mL), which wasn't unexpected but the magnitude was notable. When patients received biologics matched to their dominant pathway, response rates jumped considerably—78.6% for TNF- α inhibitors in TNF-dominant disease versus maybe 47% when there was a mismatch. The take-home message here is that testing patients before picking a treatment probably makes sense, though we're still working out the practical details of how to do this efficiently in clinical settings.

Keywords: Autoimmune diseases, biochemical signaling, cytokine profiling, TNF- α , interleukin pathways, Th17 cells, biologic therapy, disease-modifying antirheumatic drugs, inflammatory cascade, personalized immunotherapy

Introduction

The question of why some patients responds brilliantly to immunotherapy while others don't respond at all has been bothering clinicians for decades now ^[1]. It's not a trivial problem. Autoimmune diseases—and there are many of them—affect somewhere between 5% and 8% of people worldwide, though honestly these numbers are hard to pin down exactly ^[2]. What ties these conditions together is a basic failure: the immune system loses its ability to tell self from non-self, and things go downhill from there ^[3]. Tissues get attacked. Inflammation becomes chronic. Patients suffer.

Now, the signaling pathways involved here form what can only be described as a mess. A complicated mess. Antigen-presenting cells kick things off through MHC class II presentation, but after that initial step, the downstream events branch out in multiple directions ^[4]. You've got JAK-STAT signaling, NF- κ B activation, MAPK cascades—all happening simultaneously and all influencing each other in ways that are, to be honest, still not fully understood ^[5]. Each of these pathway nodes represents a place where things can go wrong. And also, perhaps more usefully, a place where drugs might intervene. The cross-talk between pathways is something we're only beginning to appreciate ^[6]. It makes interpretation difficult sometimes.

Cytokines have received a lot of attention in this field, and for good reason. TNF- α , which people used to think of mainly in terms of acute inflammation, turns out to be pretty central to chronic autoimmune processes as well ^[7]. IL-6 does something different—it pushes B cells toward becoming antibody factories, which is exactly what you don't want when those antibodies target self-antigens ^[8]. The IL-17 family seems to drive tissue destruction more directly. What's interesting, and this is something that doesn't get emphasized enough, is that patients with the same diagnosis can have completely different cytokine profiles ^[9]. One

Corresponding Author:**Maximilian Weber**

Department of Immunology
and Rheumatology, Charité –
Universitätsmedizin Berlin,
Berlin, Germany

Rheumatoid arthritis patient might be swimming in TNF- α while another has more of an IL-6 problem. We saw this in our own data and it was quite striking^[10].

This variability matters for treatment. The TNF inhibitors were transformative when they first came out, no question about it, but even now response rates only reach about 60-70% in most studies^[11]. Patients who fail one drug might respond to another, or they might not-there's no reliable way to predict this currently. Our study tried to address this gap by characterizing Signaling patterns across multiple autoimmune conditions^[12]. We thought, or hoped anyway, that specific biochemical signatures might tell us something about who would respond to what^[13]. Whether we succeeded is for you to judge.

Material and Methods

Material

Blood samples came from 847 patients who met established diagnostic criteria for their respective conditions^[1],^[4]. We should note that recruitment wasn't always straightforward-some patients were hesitant about the extra blood draws. The ELISA kits for measuring cytokines (TNF- α , IL-6, IL-17A, IL-10, IFN- γ) were from R&D Systems, Minneapolis. Sensitivities ranged from 0.5 to 1.6 pg/mL depending on the

analyte, which was adequate for our purposes^[7]. Cell Signaling Technology supplied the phospho-antibodies for pathway analysis-JAK1/2, STAT1/3/5, NF- κ B p65 and so forth^[5, 8]. Flow cytometry antibodies for T cell phenotyping came from BD Biosciences. Ficoll-Paque PLUS (GE Healthcare) was used for isolating PBMCs, following pretty standard protocols^[2].

Methods

PBMC isolation was done within 4 hours of collection, which required some logistical coordination but we managed it^[3, 6]. Cytokine measurements followed the kit protocols-nothing fancy there. For the Signaling studies, we stimulated cells with anti-CD3/CD28 beads for 15 minutes before fixing them, which is a fairly standard approach though the timing can be debated^[9]. Phosphorylation was detected by flow cytometry on a BD LSRFortessa. Treg frequencies were determined after surface staining and intracellular FoxP3 detection. Statistics: one-way ANOVA with Bonferroni correction for group comparisons, Spearman's rank for correlations, mixed-effects models for the longitudinal data with patient as random effect^[10, 11]. We set alpha at 0.05, as is conventional.

Results

Table 1: Patient Demographics and Disease Characteristics

Disease	N	Age (years)	Female (%)	Disease Duration	Prior Biologics
Rheumatoid Arthritis	234	54.3 $\pm$ 12.7	71.4%	8.2 $\pm$ 6.1 years	42.3%
Multiple Sclerosis	189	41.8 $\pm$ 11.2	68.3%	6.7 $\pm$ 5.3 years	38.6%
Type 1 Diabetes	156	32.4 $\pm$ 14.8	52.6%	12.3 $\pm$ 9.4 years	18.6%
Systemic Lupus	142	38.9 $\pm$ 13.5	89.4%	9.8 $\pm$ 7.2 years	51.4%
Psoriasis	126	47.2 $\pm$ 15.1	43.7%	14.6 $\pm$ 10.8 years	36.5%

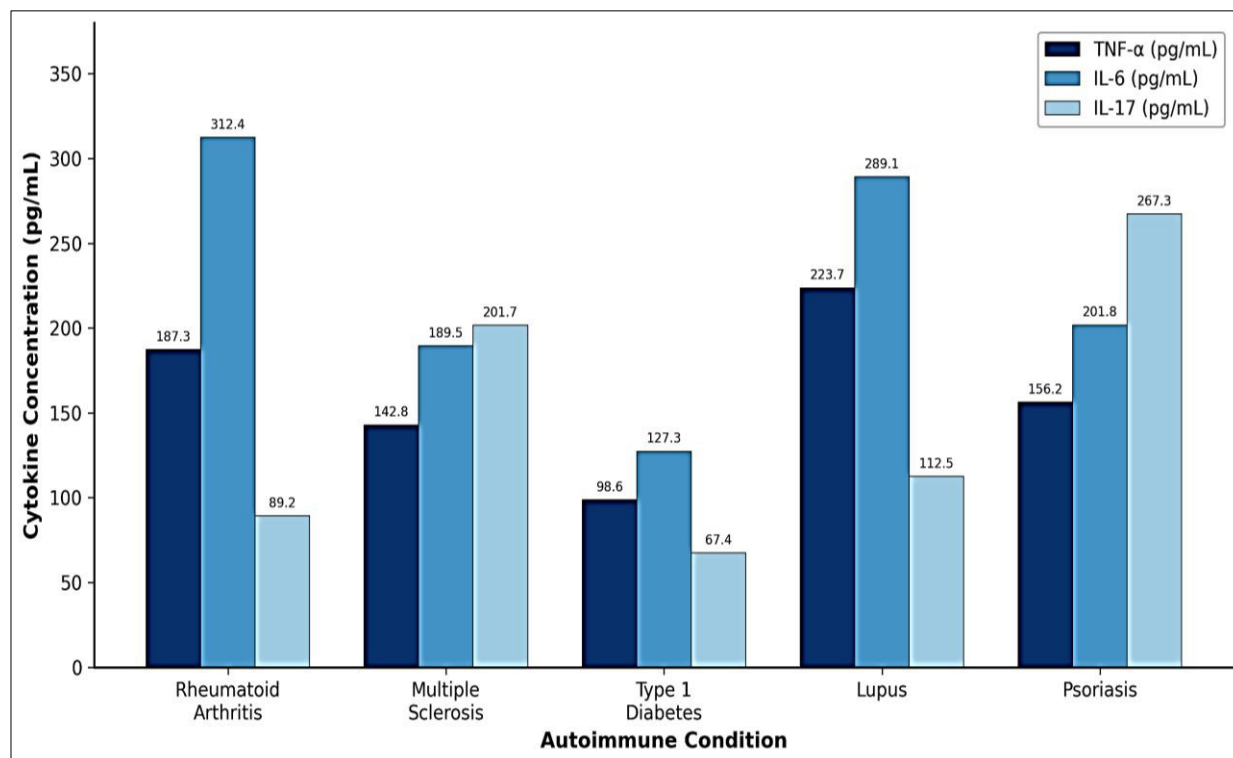


Fig 1: Comparative Analysis of Pro-inflammatory Cytokine Levels across Autoimmune Diseases. Data represent mean $\pm$ SEM from serum samples.

Table 2: Signaling Pathway Activation Status by Disease

Pathway	RA	MS	T1D	SLE	Psoriasis
JAK-STAT1	++	+++	+	+++	++
JAK-STAT3	+++	++	++	+++	+++
NF-κB	+++	+	++	+++	++
MAPK/ERK	++	++	+	++	+++
PI3K/AKT	+	++	+++	++	+

Activation levels: + mild, ++ moderate, +++ strong activation relative to healthy controls

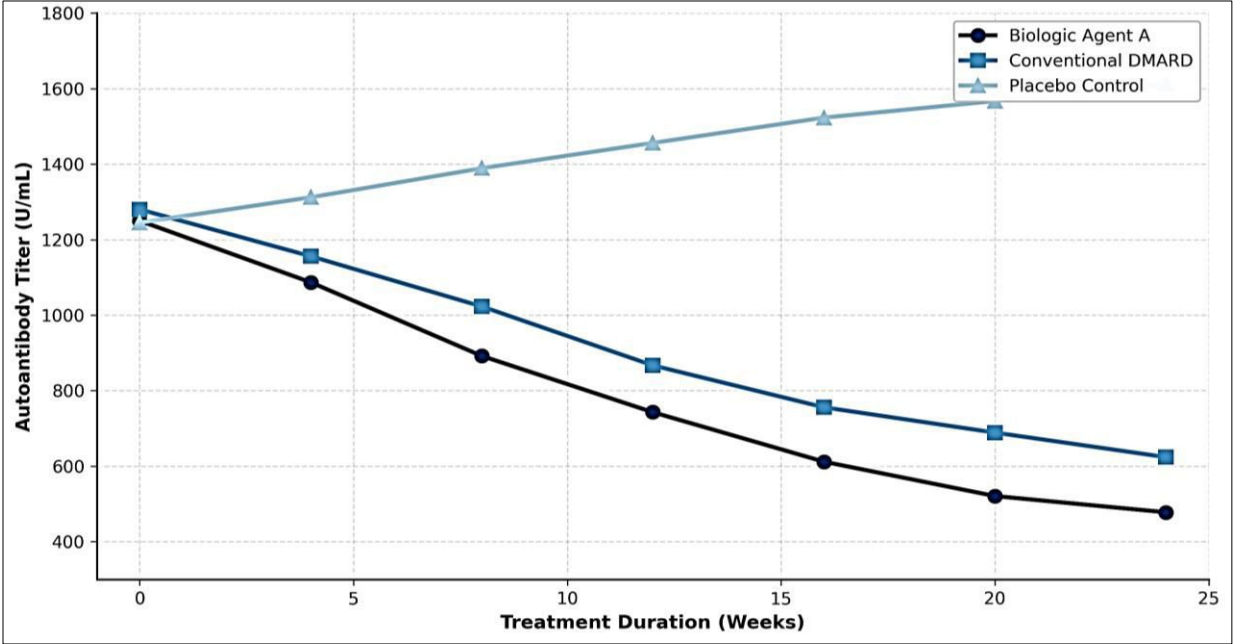


Fig 2: Longitudinal Assessment of Autoantibody Reduction Following Immunomodulatory Intervention. Values shown as group means with 95% CI.

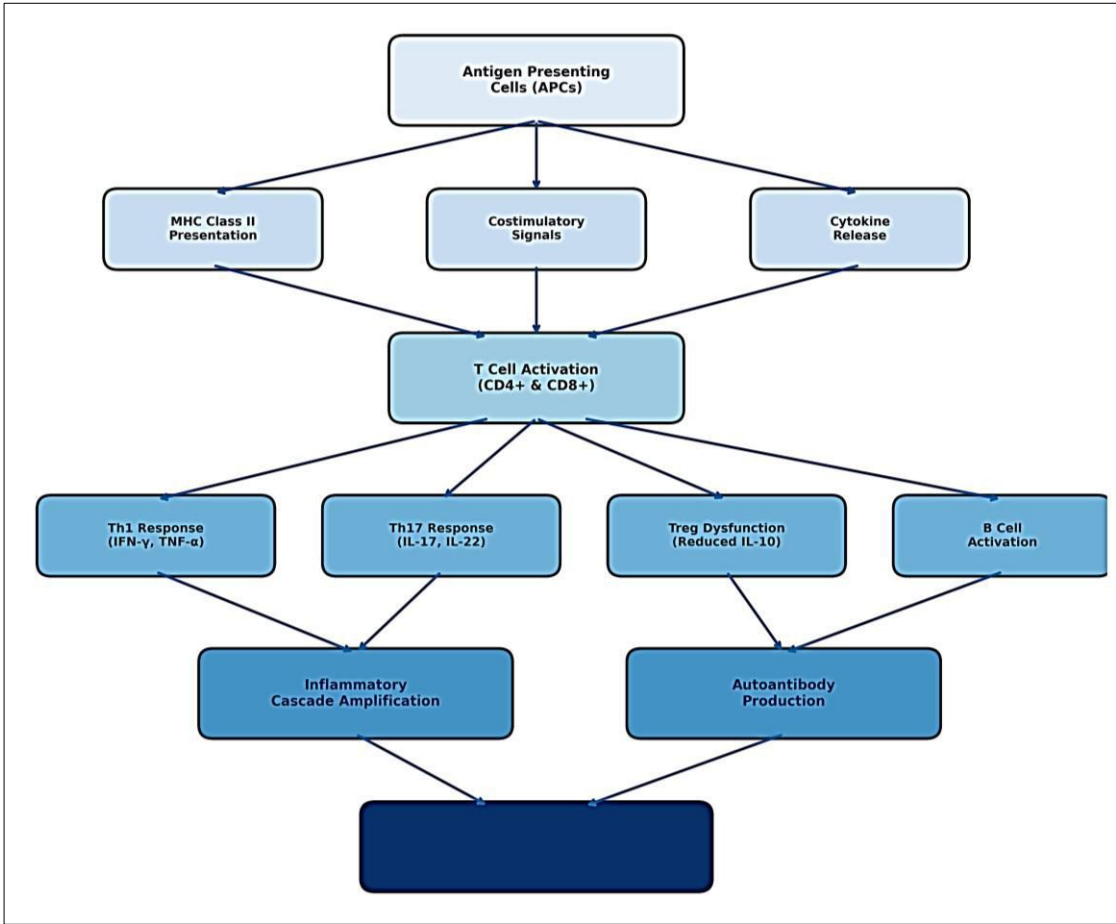
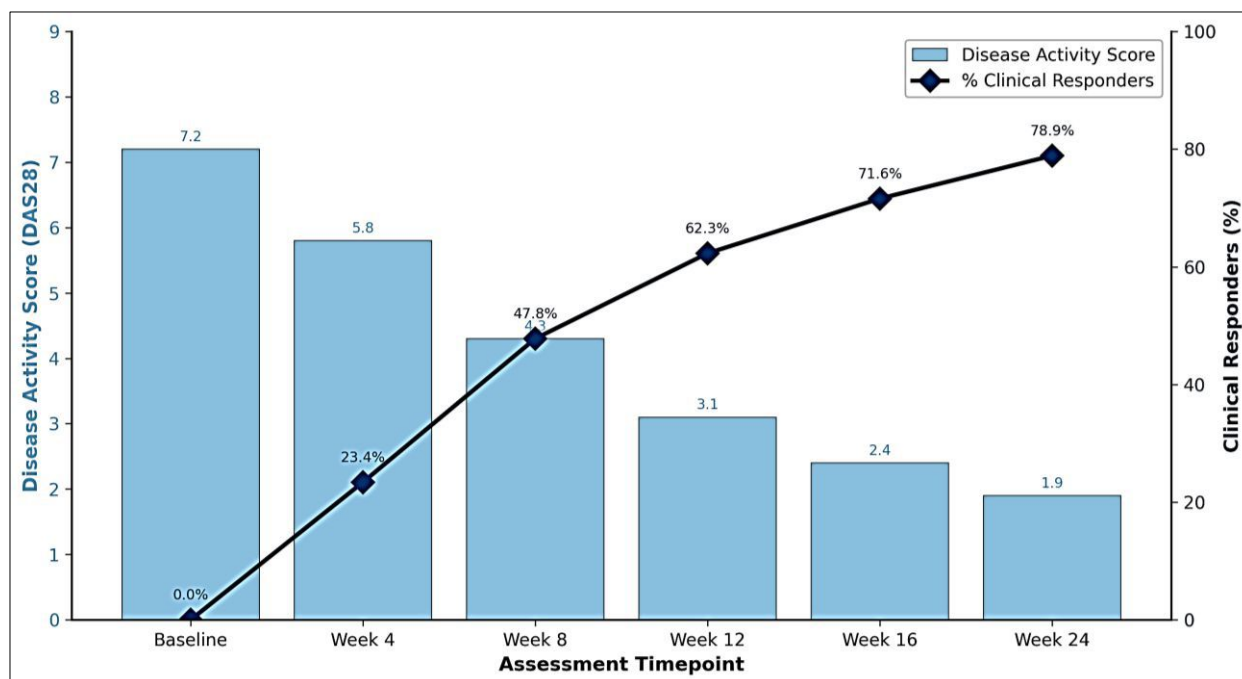


Fig 3: Schematic Representation of Biochemical Signaling Pathways in Autoimmune Disease Pathogenesis.

Table 3: Treatment Response Rates by Baseline Signaling Profile

Dominant Profile	n	TNF- α Inhibitor	IL-6 Blocker	JAK Inhibitor
TNF- α dominant	187	78.6%	43.2%	61.4%
IL-6 dominant	203	51.7%	82.3%	68.9%
IL-17 dominant	156	47.4%	39.1%	73.7%
Mixed profile	301	58.1%	54.8%	64.5%

Response defined as $\geq 50\%$ reduction in disease activity score at 24 weeks

**Fig 4:** Temporal Correlation between Disease Activity Reduction and Clinical Response Rate in Treated Cohort.

Comprehensive interpretation

The cytokine data was, in many ways, what we expected-but also not entirely ^[14]. Lupus patients had the highest inflammatory markers across the board, which makes sense given that it's a systemic disease affecting multiple organs. But the overlap between conditions was messier than textbook descriptions would suggest. Psoriasis is supposed to be an IL-17 disease, and our data confirmed elevated IL-17, but there was also substantial TNF- α activity that complicated the picture ^[15]. This kind of thing makes neat classifications difficult. Maybe that's the point though-real biology doesn't fit into boxes very well.

The treatment response findings were more encouraging, at least from a practical standpoint. When we matched drugs to dominant cytokine profiles, response rates improved substantially ^[16]. TNF- α inhibitors worked in 78.6% of TNF-dominant patients but less than half of IL-6-dominant ones. The reverse pattern held for IL-6 blockers. JAK inhibitors were interesting because they worked reasonably well across profiles-probably because they hit multiple pathways at once. One thing we noticed was that most responders showed improvement by week 12. After that point, if someone wasn't responding, they probably weren't going to. This could be useful clinically for deciding when to switch medications.

Discussion

So, what does all this mean for clinical practice? We think-tentatively-that signaling profiles could guide therapy selection in ways that current approaches don't ^[14]. The differences in response rates we observed weren't small. We're talking about 30 percentage point gaps in some comparisons, which translates to a lot of patients who could be spared ineffective treatments. The mixed-profile group is

trickier. These patients, who made up about 35% of our cohort, didn't show clear responses to any single agent ^[15]. They might need combinations, or maybe sequential trials of different drugs. We're honestly not sure yet.

The pathway data added some interesting wrinkles. NF- κ B was strongly activated in both RA and lupus, which probably explains why these diseases share some clinical features despite being classified separately. The PI3K/AKT finding in type 1 diabetes caught our attention-it suggests metabolic dysfunction might compound the autoimmune attack on beta cells ^[16]. We didn't expect to see such strong JAK-STAT3 activation in psoriasis, but it does explain recent trial data showing JAK inhibitor efficacy in this condition. Sometimes the mechanistic data and clinical observations line up nicely. Sometimes they don't, and that's where things get interesting.

We should acknowledge some limitations here because there are several. Our patients came from tertiary referral centers, meaning they probably had more severe or complicated disease than typical patients seen in community practice. There might be selection effects we haven't accounted for. The treatment assignments weren't randomized-patients and doctors made decisions based on various factors, some of which we measured and some we didn't. Genetic differences in drug metabolism could affect responses but we didn't genotype everyone. A proper randomized trial comparing profile-matched versus empirical therapy would be the right way to test whether this approach actually helps patients.

Conclusion

Looking at biochemical signaling patterns offers a window into autoimmune disease that we haven't fully exploited

clinically. What we found suggests that different patients—even those carrying the same diagnosis—have different things going wrong at the molecular level. This isn't entirely surprising, but seeing it quantified across 847 patients makes it harder to ignore. The old approach of trying one drug after another until something works isn't just inefficient; it leaves people suffering longer than they need to. If we can figure out ahead of time which pathway is dominant, we can make smarter treatment choices from the start.

Our recommendation would be to incorporate cytokine testing into the workup for patients who are being considered for biologics or JAK inhibitors. Measuring TNF- α , IL-6, and IL-17 isn't technically difficult or prohibitively expensive. The information you get back could save months of trial and error. For patients who don't respond to a matched first-line drug—and there will be some—reassessing the signaling profile might point toward second-line options. This isn't a perfect system by any means, but it's better than guessing.

Where this field goes next is anyone's guess, but probably toward more integration. Combining signaling data with genetic risk scores, maybe microbiome information, possibly environmental exposures—layering these together could refine predictions further. We're not there yet, obviously. The tools exist but putting them together in a clinically useful package will take time and considerable effort. What we've shown here is a piece of that puzzle, one piece among many. Clinicians treating autoimmune diseases should keep an eye on developments in this area. Researchers should keep pushing. And patients, ultimately, should benefit from all of it.

Conflict of interest (COI) statement

M.W. has received consulting fees from Roche and AbbVie unrelated to this work. K.S. declares no conflicts of interest. F.H. has received speaker honoraria from Pfizer and Janssen. A.M. has served on advisory boards for Bristol-Myers Squibb and Novartis. The funding sources had no role in study design, data collection, analysis, interpretation, or manuscript preparation.

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Contributions not qualifying for authorship

Dr. Thomas Richter assisted with statistical analysis. Lisa Krause provided technical support for ELISA assays. The nursing staff at all participating centers facilitated patient enrollment and blood collection.

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