Abstract: Anti-TNF therapy has significantly improved disease control in rheumatoid arthritis, but a fraction of rheumatoid arthritis patients do not respond to anti-TNF therapy or lose response over time. Moreover, the mechanisms underlying non-response to anti-TNF therapy remain largely unknown. To date, many single biomarkers of response to anti-TNF therapy have been published but they have not yet been analyzed as a system of interacting nodes. The aim of our study is to systematically elucidate the biological processes underlying non-response to anti-TNF therapy in rheumatoid arthritis using the gene ontologies of previously published predictive biomarkers. Gene networks were constructed based on published biomarkers and then enriched gene ontology terms were elucidated in subgroups using gene ontology software tools. Our results highlight the novel role of proteasome-mediated protein catabolic processes ($p = 2.91 \times 10^{-15}$) and plasma lipoproteins ($p = 4.55 \times 10^{-11}$) in anti-TNF therapy response. The results of our gene ontology analysis help elucidate the biological processes underlying non-response to anti-TNF therapy in rheumatoid arthritis and encourage further study of the highlighted processes.

Keywords: gene ontology; rheumatoid arthritis; treatment outcome; infliximab; adalimumab; biomarkers

1. Introduction

Rheumatoid arthritis (RA) is a common complex autoimmune disease characterized by chronic and progressive joint inflammation. Currently, first-line therapeutic approaches in rheumatoid arthritis focus on minimizing disease activity using, primarily, corticosteroids with or without disease-modifying antirheumatic drugs (DMARDs). The development of biological drugs such as monoclonal antibodies against key inflammatory cytokines has significantly improved symptom control [1] in severe rheumatoid arthritis and chronic patients failing first-line therapy. Etanercept [2] and infliximab, inhibitors of proinflammatory cytokine tumor necrosis factor alpha (anti-TNF) [3], were the first anti-TNF biological drugs indicated for rheumatoid arthritis, and later more biological drugs against TNFα were developed, including adalimumab [4], certolizumab pegol [5] and golimumab [6]. In recent years, the emergence of biosimilars of anti-TNF biological drugs has also somewhat reduced the initially high cost of anti-TNF therapy while maintaining efficacy levels comparable to those of the originator biological drugs [7].

However, despite the immense therapeutic power of anti-TNF therapy, 10–30% of patients do not respond to anti-TNF biological drugs upon therapy initiation (i.e., primary non-response) and 23–46% of responders lose response to anti-TNF therapy over time (i.e., secondary non-response) [8]. Non-response to anti-TNF therapy usually represents loss of
disease control in patients with severe rheumatoid arthritis, as well as unnecessary exposure to potentially severe adverse effects of anti-TNF drugs and inefficient use of expansive biological therapeutics. Patients who fail to respond to anti-TNF drugs may switch to a different biological drug, such as anakinra, rituximab or sarilumab [9]. Even so, other biological drugs face similar challenges to anti-TNF drugs in terms of non-response [1,10,11]. Therefore, disease-modifying antirheumatic drugs (DMARDs) remain the long-term therapy of choice alongside corticosteroids for disease flares, both of which are known to have significant long-term adverse effects [12].

Predicting non-response to anti-TNF therapy based on the patient’s clinical and biological data would allow targeted therapy with higher efficacy and fewer adverse effects, as well as cost-efficient use of therapeutics. Physicians could determine if and when to switch anti-TNF therapeutics or whether it would be more effective to switch to biological drugs with different therapeutic targets. To date, response to anti-TNF therapy has been intensively studied and several DNA, RNA and protein response biomarkers with low to moderate predictive accuracy have been identified. However, despite the many published anti-TNF response biomarkers, the biological processes underlying non-response to anti-TNF therapy in RA remain largely unknown. Improving the understanding of the mechanisms underlying non-response to anti-TNF drugs on a molecular level would allow the development of novel therapeutic strategies to prevent non-response or the discovery of novel pharmaceutical targets for drug development. To this end, we reviewed already published genomic, transcriptomic and proteomic markers of response and non-response to anti-TNF biological drugs in rheumatoid arthritis and performed a gene ontology analysis to help elucidate biological processes linked to response and non-response to anti-TNF therapy.

2. Materials and Methods

2.1. Literature Search

To perform a comprehensive review of the literature on anti-TNF therapy response biomarkers, we searched the PubMed database using a combination of terms defining disease, drug, response, biomarker type and exclusion criteria. To prevent Mesh terms missing synonyms, we employed a combination of both Mesh terms and equivalent non-Mesh keywords. The final search query was defined as a combination of the following term groups:

- Disease terms: “Arthritis, Rheumatoid” (Mesh) OR (“rheumatoid” AND “arthritis”);
- Drug terms: “infliximab” OR “adalimumab” OR “etanercept” OR “golimumab” OR “certolizumab pegol” OR “Tumor Necrosis Factor-alpha/antagonists and inhibitors” (Mesh) OR “TNFA inhibitor” OR “TNF inhibitor” OR “anti-TNF therapy” OR “anti-TNFα therapy” OR “Treatment Outcome” (Mesh);
- Response terms: “predictor” OR “responder” OR “nonresponder” OR “non-responder” OR “therapy outcome” OR “therapy response” OR “response biomarker” OR “outcome biomarker” OR “response predictor” OR “outcome predictor”;
- Biomarker terms: genetics OR genomics OR transcriptomics OR proteomics OR metabolomics OR “DNA methylation”;
- Exclusion terms: NOT (“tocilizumab” OR dose OR dosing).

Studies were included based on the following inclusion criteria:

- Published between the years 2002 and 2022;
- The study used well-defined response criteria (e.g., those included in the Disease Activity Score in 28 Joints, also known as ΔDAS28);
- Biomarkers were analyzed prior to therapy initiation and, if applicable, after therapy (e.g., gene expression and serum protein levels);
- Quantitative biomarkers were reported with a clearly defined direction of association (e.g., gene expression defined as up-regulated or down-regulated, not merely “associated”).
In this gene ontology study, we did not make any additional distinctions based on the anti-TNF drugs used or on whether patients were anti-TNF naive or not.

2.2. Subset Definition

Subsets for gene ontology (GO) analysis were defined based on biomarker type. Preliminary subset analysis revealed no significant differences between the gene ontology terms of biomarkers measured in synovial fluid and those measured in sera. For this reason, we did not make any distinctions based on biomarker measurement locations.

Potential therapeutic targets can be either stimulated or blocked. In general, processes that are up-regulated in responders or down-regulated in non-responders could be stimulated to achieve better response or even restore response. Similarly, processes that are down-regulated in responders or up-regulated in non-responders can be blocked. Following this reasoning, we created two additional separate groups for RNA and protein biomarkers. The first group (\_UP\_R\_DO\_N) contains biomarkers reported either as up-regulated in responders or down-regulated in non-responders; the second group (\_DO\_R\_UP\_N) contain biomarkers down-regulated in responders or up-regulated in non-responders.

To enhance biological process discovery with gene ontology analysis, gene networks were constructed. In this study, “gene network” refers to a set of interacting biomarkers produced from a list of biomarkers of interest (i.e., previously published anti-TNF response biomarkers). Biomarkers interacting with at least two biomarkers of interest were obtained from BIOGRID [13,14] using the biogridR package [15] for R (version 4.1.1, R Core Team, Vienna, Austria) [16].

Subset names are defined in Table 1.

| Subset Name                  | Biomarkers Included in Subset                                                                 |
|------------------------------|------------------------------------------------------------------------------------------------|
| DNA                          | All DNA biomarkers                                                                             |
| RNA                          | All RNA biomarkers                                                                             |
| RNA\_UP\_R\_DO\_N           | RNA biomarkers up-regulated in responders or down-regulated in non-responders                  |
| RNA\_DO\_R\_UP\_N           | RNA biomarkers up-regulated in non-responders or down-regulated in responders                  |
| PRO                          | All protein biomarkers                                                                          |
| PRO\_UP\_R\_DO\_N           | Protein biomarkers up-regulated in responders or down-regulated in non-responders              |
| PRO\_DO\_R\_UP\_N           | Protein biomarkers up-regulated in non-responders or down-regulated in responders              |
| DNA\_BIO                     | BIOGRID network based on DNA biomarkers                                                         |
| RNA\_BIO                     | BIOGRID network based on RNA biomarkers                                                         |
| RNA\_UP\_R\_DO\_N\_BIO      | BIOGRID network based on RNA biomarkers up-regulated in responders or down-regulated in non-responders |
| RNA\_DO\_R\_UP\_N\_BIO      | BIOGRID network based on RNA biomarkers up-regulated in non-responders or down-regulated in responders |
| PRO\_BIO                    | BIOGRID network based on protein biomarkers                                                     |
| PRO\_UP\_R\_DO\_N\_BIO      | BIOGRID network based on protein biomarkers up-regulated in responders or down-regulated in non-responders |
| PRO\_DO\_R\_UP\_N\_BIO      | BIOGRID network based on protein biomarkers up-regulated in non-responders or down-regulated in responders |

2.3. Gene Ontology Analysis

Gene ontology analysis was performed using the software package CytoScape (v3.8.2, CytoScape Team) [17] with the integrated application ClueGO (v2.5.8, Laboratory of Inte-
ClueGO analysis was performed using the following parameters and selected options:

- Ontology/pathways selected:
  - Biological Process (13 May 2021);
  - Cellular Component (13 May 2021);
  - Molecular Function (13 May 2021);
- Evidence selected: only All_Experimental.

Moreover, comparative gene ontology analysis was employed to estimate GO term specificity between different subsets (e.g., _UP_RE_DO_NR vs. _UP_NR_DO_RE). Statistical significance was defined as a \( p \)-value lower than \( 5 \times 10^{-2} \) after Bonferroni step-down correction (the default selection in ClueGO v2.5.8).

Gene ontology analysis results were visualized using default Cytoscape settings and freely available style options.

### 3. Results

#### 3.1. Literature Search

Using the defined search query (see Materials and Methods—Literature Search), we obtained 185 results in the PubMed database. Based on the inclusion criteria, 125 studies were included in the gene ontology analysis. Among the 125 studies, 61 studies reported DNA biomarkers, 15 studies reported RNA biomarkers, 39 studies reported protein biomarkers, while 10 studies reported response biomarkers that could not be categorized as DNA, RNA or protein biomarkers as they were cell counts, nuclear magnetic resonance (NMR) spectra or metabolomic markers. In addition, five studies reported biomarkers at several molecular levels.

Use of technologies to comprehensively study the genome, transcriptome and proteome remains uncommon, but it has become more common in recent years. Among the 61 DNA biomarker studies, 8 employed next-generation sequencing (NGS) technology and 3 out of 15 RNA biomarker studies employed RNA sequencing (RNAseq). Similarly, 7 out of 39 protein biomarker studies used liquid chromatography with mass spectrometry (LC–MS/MS) for biomarker discovery.

#### 3.2. Biomarker Collection

The biomarkers extracted from the studies gathered from the literature are shown in Table 2 (DNA biomarkers), Table 3 (RNA biomarkers) and Table 4 (protein biomarkers). For gene ontology (GO) analysis, only biomarkers indexed in GO datasets can be processed. To remove potential duplicate biomarkers and obsolete gene names, we used the g:Convert Gene ID Converter tool [19] to update the biomarker names to the most recent ones. Finally, biomarkers that could not be reliably assigned to a gene with GO definitions were excluded (e.g., intergenic genetic variants).

#### Table 2. DNA biomarkers of response to anti-TNF therapy in RA.

| Study | Associated Gene |
|-------|-----------------|
| Criswell, L.A. et al., 2004 [20] | TNF, LTA, HLA-DRB1 |
| Lee, Y.H. et al., 2006 [21] | TNF |
| Ongaro, A. et al., 2008 [22] | TNFSFR1B |
| Jančić, I. et al., 2013 [23] | IL6 |
| Lee, Y.H. et al., 2014 [24] | IL6 |
| Lee, Y.H. et al., 2016 [25] | PTPRC, FCGR2A |
| Study                                      | Associated Gene |
|-------------------------------------------|-----------------|
| Schotte, H. et al., 2015 [26]             | IL6             |
| Pappas, D.A. et al., 2013 [27]            | CCL21 CD28      |
| Morales-Lara, M.J. et al., 2012 [28]      | TRAILR1 TNFR1A  |
| Pers, Y.M. et al., 2014 [29]              | TNFSFR1B        |
| Iwaszko, M. et al., 2016 [30]             | KLRD1 KLRC1     |
| O’Rielly, D.D. et al., 2009 [31]          | TNF             |
| Ferreiro-Iglesias, A. et al., 2016 [32]   | PTPRC IL10      |
| Julià, A. et al., 2016 [33]               | MED15           |
| Kang, C.P. et al., 2005 [34]              | TNF             |
| Seitz, M. et al., 2007 [35]               | TNF             |
| Iannaccone, C.K. et al., 2011 [36]        | PTPRC           |
| Dávila-Fajardo, C.L. et al., 2014 [37]    | IL6             |
| Montes, A. et al., 2014 [38]              | FCGR2A          |
| Bowes, J.D. et al., 2009 [39]             | MAP3K1 MAP3K14  |
| Miceli-Richard, C. et al., 2008 [40]      | HLA-DRB1        |
| Tsukahara, S. et al., 2008 [41]           | FCGR3A          |
| Cañete, J.D. et al., 2009 [42]            | FCGR2A FCGR3A   |
| Potter, C. et al., 2010 [43]              | MYD88 CHUK      |
| Coulthard, L.R. et al., 2011 [44]         | MAP2K6 MSK1 MSK2 MAPK14 |
| Acosta-Colman, I. et al., 2013 [45]       | PDE3A           |
| Dávila-Fajardo, C.L. et al., 2015 [46]    | FCGR2A          |
| Sun, Y. et al., 2017 [47]                 | FCGR2A FCGR3A   |
| Morales-Lara, M.J. et al., 2010 [48]      | FCGR3A          |
| Lee, Y.H. et al., 2010 [49]               | TNF             |
| Liu, C. et al., 2008 [50]                 | LMO4 GBP6 CERS6 ARAP2 QKI PON1 IFNK MOB3B CST5 |
Table 2. Cont.

| Study                                      | Associated Gene |
|--------------------------------------------|-----------------|
| Tan, R.J. et al., 2010 [51]                | AFF3            |
|                                            | CD226           |
| Plant, D. et al., 2011 [52]                | EYA4            |
|                                            | PDZD2           |
| McGeough, C.M. et al., 2012 [53]           | HLA-C           |
| Krintel, S.B. et al., 2012 [54]            | CD19            |
|                                            | STXBP6          |
| Plant, D. et al., 2012 [55]                | PTPRC           |
| Cui, J. et al., 2013 [56]                  | CD84            |
| Cui, J. et al., 2010 [57]                  | PTPRC           |
| Sode, J. et al., 2014 [58]                 | NLRP3           |
| Umicévić Mirkov, M. et al., 2013 [59]      | CNTN5           |
|                                            | NUBPL           |
| Canhão, H. et al., 2015 [60]               | TRAF1           |
| Avila-Pedretti, G. et al., 2015 [61]       | FCGR2A          |
| Schotte, H. et al., 2015 [62]              | IL10            |
| Sode, J. et al., 2015 [63]                 | TLR1            |
|                                            | TLR5            |
|                                            | NLRP3           |
| Honne, K. et al., 2016 [64]                | MAP3K7          |
|                                            | BACH2           |
|                                            | WDR27           |
|                                            | GFRA1           |
| Jančić, I. et al., 2015 [65]               | TNF             |
|                                            | IL6             |
| Folkersen, L. et al., 2016 [66]            | MAFB            |
| Gebura, K. et al., 2017 [67]               | TLR9            |
|                                            | NFKB1           |
| Nishimoto, T. et al., 2014 [68]            | TRAF1           |
| Sarsour, K. et al., 2013 [69]              | FCGR3A          |
| Vasilopoulos, Y. et al., 2011 [70]         | TNFRSF1B        |
|                                            | TNF             |
|                                            | TNFRSF1A        |
| Rooryck, C. et al., 2008 [71]              | TNFRSF1B        |
| Cuchacovich, M. et al., 2006 [72]          | TNF             |
| Tutunca, Z. et al., 2005 [73]              | FCGR3A          |
| Sode, J. et al., 2018 [74]                 | IRAK3           |
|                                            | CHUK            |
|                                            | MYD88           |
|                                            | NFKB1B          |
|                                            | NLRP3           |
| Iwaszko, M. et al., 2018 [75]              | NKG2D           |
| Skapenko, A. et al., 2019 [76]             | HLA-DRB1        |
|                                            | IL4R            |
|                                            | FCGR2B          |
| Spiliopoulou, A. et al., 2019 [77]         | CD40            |
|                                            | ENTPD1          |
### Table 2. Cont.

| Study                        | Associated Gene |
|------------------------------|-----------------|
| Wielińska, J. et al., 2020   | RANK, RANKL     |
| Gibson, D.S. et al., 2021    | CD226, HLA-DRB1 |
| Iwaszko, M. et al., 2021     | IL33            |

### Table 3. RNA biomarkers of response to anti-TNF therapy in RA.

| Study                        | Gene          | Association Direction          |
|------------------------------|---------------|-------------------------------|
| Stuhlmüller, B. et al., 2010 | CD11C         | Up-regulated in responders    |
| Sekiguchi, N. et al., 2008   | HLA-DQA1      | Down-regulated in non-responders |
|                             | IGHMI         | Down-regulated in non-responders |
|                             | APIS2         | Up-regulated in non-responders |
| Wright, H.L. et al., 2015    | IFNG          | Up-regulated in responders    |
| Wright, H.L. et al., 2016    | CMPK2         | Up-regulated in responders    |
|                             | IFIT1B        | Up-regulated in responders    |
|                             | RNASE3        | Up-regulated in responders    |
| Tsuzaka, K. et al., 2010     | ADAMTS5       | Down-regulated in responders  |
| Oliveira, R.D. et al., 2012  | CCL4          | Up-regulated in responders    |
|                             | CD83          | Up-regulated in responders    |
|                             | BCL2A1        | Up-regulated in responders    |
| Lequerré, T. et al., 2006    | CYP3A4        | Down-regulated in responders  |
|                             | AKAP9         | Down-regulated in responders  |
|                             | LAMR1         | Down-regulated in responders  |
|                             | FBXO5         | Down-regulated in responders  |
|                             | RASGRP3       | Down-regulated in responders  |
|                             | PFKFB4        | Down-regulated in responders  |
|                             | HLA-DPB1      | Down-regulated in responders  |
|                             | PSMB9         | Down-regulated in responders  |
|                             | EPS15         | Down-regulated in responders  |
|                             | MTCBP-1       | Down-regulated in responders  |
|                             | MRPL22        | Up-regulated in responders    |
|                             | MCP           | Up-regulated in responders    |
|                             | KNG1          | Up-regulated in responders    |
|                             | AADAT         | Up-regulated in responders    |
Table 3. Cont.

| Study                        | Gene     | Association Direction |
|------------------------------|----------|------------------------|
| Koczan, D. et al., 2008 [88] | TNFAIP3  | Down-regulated in responders |
|                              | NFKB1A   | Down-regulated in responders |
|                              | RUNX1    | Up-regulated in responders |
|                              | ZFP36L2  | Down-regulated in responders |
|                              | IL1B     | Down-regulated in responders |
|                              | IL1B     | Down-regulated in responders |
|                              | CCL4     | Down-regulated in responders |
|                              | CCL3     | Down-regulated in responders |
|                              | CXCL2    | Down-regulated in responders |
|                              | ADAM12   | Down-regulated in responders |
|                              | SCN2B    | Up-regulated in responders |
|                              | PDE4B    | Down-regulated in responders |
|                              | RAPGEF1  | Down-regulated in responders |
|                              | MYO10    | Down-regulated in responders |
|                              | PTPRD    | Up-regulated in responders |
|                              | PDE4B    | Down-regulated in responders |
|                              | LGALS13  | Up-regulated in responders |
|                              | CHST3    | Down-regulated in responders |
|                              | LUC7L3   | Up-regulated in responders |
|                              | PPP1R15A | Down-regulated in responders |
|                              | ADM      | Down-regulated in responders |
|                              | CHRND    | Down-regulated in responders |
|                              | PIGO     | Down-regulated in responders |
|                              | RNF19B   | Down-regulated in responders |
|                              | FSD1     | Down-regulated in responders |
| van Baarsen, L.G. et al., 2010 [89] | OAS1     | Up-regulated in non-responders |
|                              | LGALS3BP | Up-regulated in non-responders |
|                              | MX2      | Up-regulated in non-responders |
|                              | OAS2     | Up-regulated in non-responders |
|                              | SERPING1 | Up-regulated in non-responders |
| Toonen, E.J. et al., 2012 [90] | HIRIP3   | Down-regulated in responders |
|                              | TPM1     | Up-regulated in responders |
|                              | NPR1L2   | Down-regulated in responders |
|                              | CLIC3    | Down-regulated in responders |
|                              | PTGS2    | Up-regulated in responders |
|                              | G0S2     | Up-regulated in responders |
|                              | PIGV     | Down-regulated in responders |
|                              | HIF1A    | Up-regulated in responders |
|                              | ZBTB6    | Down-regulated in responders |
Table 3. Cont.

| Study                      | Gene    | Association Direction   |
|----------------------------|---------|-------------------------|
| Toonen, E.J. et al., 2012  | RANBP17 | Up-regulated in responders |
|                            | PCGF5   | Up-regulated in responders |
|                            | SESTD1  | Up-regulated in responders |
|                            | GPD2    | Up-regulated in responders |
|                            | HERPUD2 | Up-regulated in responders |
|                            | DND1    | Down-regulated in responders |
|                            | SH2D2A  | Down-regulated in responders |
|                            | EIF4E2  | Down-regulated in responders |
|                            | GTPBP2  | Up-regulated in responders |
|                            | TPRA1   | Down-regulated in responders |
|                            | GRAMD1B | Up-regulated in responders |
|                            | PPP1R15A| Up-regulated in responders |
|                            | PMAIP1  | Up-regulated in responders |
|                            | RAPGEF1 | Up-regulated in responders |
|                            | CSRNP1  | Up-regulated in responders |
|                            | TMOD2   | Up-regulated in responders |
|                            | EGR2    | Up-regulated in responders |
|                            | DUSP1   | Up-regulated in responders |
|                            | MTURN   | Up-regulated in responders |
|                            | EGR3    | Up-regulated in responders |
|                            | SQSTM1  | Up-regulated in responders |
|                            | RAMP3   | Down-regulated in responders |
|                            | PDE3A   | Up-regulated in responders |
|                            | VEPH1   | Up-regulated in responders |
|                            | GBP7    | Up-regulated in responders |
|                            | PSTPIP2 | Up-regulated in responders |
|                            | FAM221A | Down-regulated in responders |
|                            | ZNF2    | Down-regulated in responders |
|                            | MED12L  | Up-regulated in responders |
|                            | OSM     | Down-regulated in responders |
|                            | TMEM186 | Down-regulated in responders |
|                            | PKHD1L1 | Up-regulated in responders |
|                            | OR6C74  | Down-regulated in responders |
|                            | GPN2    | Down-regulated in responders |
|                            | DDX39B  | Down-regulated in responders |
|                            | UNQ5840 | Down-regulated in responders |
|                            | C15orf40| Down-regulated in responders |
|                            | CMIP    | Up-regulated in responders |
|                            | KCNJ13  | Down-regulated in responders |
|                            | SLC7A6OS| Down-regulated in responders |
| Study | Gene | Association Direction |
|-------|------|-----------------------|
| Toonen, E.J. et al., 2012 [90] | ELOVL4 | Down-regulated in responders |
|       | UQCRFS1 | Down-regulated in responders |
|       | NBN | Up-regulated in responders |
|       | BEX2 | Down-regulated in responders |
|       | YPEL5 | Up-regulated in responders |
|       | FAIM | Down-regulated in responders |
|       | STAT1 | Up-regulated in responders |
|       | CXCL8 | Down-regulated in responders |
|       | PIH1D2 | Down-regulated in responders |
|       | EDC3 | Down-regulated in responders |
|       | TNFAIP3 | Up-regulated in responders |
|       | FSCN1 | Down-regulated in responders |
|       | MGLL | Up-regulated in responders |
|       | GCNT2 | Up-regulated in responders |
|       | EGF | Up-regulated in responders |
|       | COLGALT2 | Down-regulated in responders |
|       | HOPX | Down-regulated in responders |
|       | NT5C3A | Up-regulated in responders |
|       | RNF11 | Up-regulated in responders |
|       | SLK | Up-regulated in responders |
|       | TAP2 | Up-regulated in responders |
|       | GBP1 | Up-regulated in responders |
|       | GBP5 | Up-regulated in responders |
|       | XRN1 | Up-regulated in responders |
|       | PTGDS | Down-regulated in responders |
|       | TAS2R50 | Up-regulated in responders |
|       | HSPC159 | Up-regulated in responders |
|       | ARL6 | Down-regulated in responders |
|       | PDE4B | Up-regulated in responders |
|       | OR2L3 | Down-regulated in responders |
|       | NR4A2 | Up-regulated in responders |
|       | PALD1 | Down-regulated in responders |
|       | OGG1 | Down-regulated in responders |
|       | ADGRE5 | Up-regulated in responders |
|       | FRMD3 | Up-regulated in responders |
|       | LRRQ3 | Down-regulated in responders |
|       | RAD23A | Down-regulated in responders |
|       | APP | Up-regulated in responders |
|       | PXT1 | Down-regulated in responders |
|       | MPP7 | Up-regulated in responders |
| Study                      | Gene  | Association Direction |
|---------------------------|-------|------------------------|
| Toonen, E.J. et al., 2012 [90] | NEXN  | Up-regulated in responders |
|                           | GMPR  | Up-regulated in responders |
|                           | UVRAG | Up-regulated in responders |
|                           | ADAMTS1 | Down-regulated in responders |
|                           | ATP6V0A2 | Down-regulated in responders |
|                           | CATSPER3 | Down-regulated in responders |
|                           | C5    | Up-regulated in responders |
|                           | MAP4K2 | Up-regulated in responders |
|                           | GCH1  | Up-regulated in responders |
|                           | ATP6V0E2 | Down-regulated in responders |
|                           | FBXO10 | Down-regulated in responders |
|                           | ZNF425 | Down-regulated in responders |
|                           | HSCB  | Down-regulated in responders |
|                           | GTF2F2 | Up-regulated in responders |
|                           | PGK1  | Down-regulated in responders |
|                           | STAT2 | Up-regulated in responders |
|                           | PCSK6 | Up-regulated in responders |
|                           | TMEM268 | Up-regulated in responders |
|                           | PPCDC | Up-regulated in responders |
|                           | GSX1  | Down-regulated in responders |
| Cui, J. et al., 2013 [56]  | CD84  | Up-regulated in responders |
|                           | FOXA2 | Up-regulated in non-responders |
|                           | ERBB2 | Up-regulated in non-responders |
|                           | IL11 | Up-regulated in non-responders |
|                           | MAP2K3 | Up-regulated in non-responders |
|                           | NF1   | Down-regulated in non-responders |
|                           | S100A9 | Down-regulated in non-responders |
|                           | S100A8 | Down-regulated in non-responders |
| Thomson, T.M. et al., 2015 [91] | MST1R | Down-regulated in non-responders |
|                           | NOS2  | Down-regulated in non-responders |
|                           | NR2F6 | Down-regulated in non-responders |
|                           | PPARG | Up-regulated in non-responders |
|                           | MEIS1 | Up-regulated in non-responders |
|                           | DPPA4 | Up-regulated in non-responders |
|                           | MBID1 | Down-regulated in non-responders |
|                           | CDK2  | Up-regulated in non-responders |
| Folkersen, L. et al., 2016 [66] | SORBS3 | Down-regulated in responders |
|                           | AKAP9 | Down-regulated in responders |
| Study                        | Gene   | Association Direction |
|-----------------------------|--------|-----------------------|
| Póliska, S. et al., 2019 [92]| TMEM176A | Up-regulated in responders |
|                             | TMEM176B | Up-regulated in responders |
|                             | PLSCR1 | Up-regulated in responders |
|                             | IFI44 | Up-regulated in responders |
|                             | LIN7A | Down-regulated in responders |
|                             | CREB5 | Down-regulated in responders |
|                             | ENTPD1 | Down-regulated in responders |
|                             | ITGB7 | Up-regulated in responders |
|                             | HLA-DMA | Up-regulated in responders |
|                             | IL6R | Down-regulated in responders |
|                             | SLC8A1 | Down-regulated in responders |
|                             | IL1B | Down-regulated in responders |
|                             | HLA-DOB | Up-regulated in responders |
|                             | MGAM | Down-regulated in responders |
|                             | TRAF5 | Up-regulated in responders |
|                             | AES | Up-regulated in responders |
|                             | E2F5 | Up-regulated in responders |
|                             | ZFYVE16 | Down-regulated in responders |
|                             | HLA-DOA | Up-regulated in responders |
|                             | TLR8 | Down-regulated in responders |
|                             | STAP1 | Up-regulated in responders |
|                             | TGM3 | Down-regulated in responders |
|                             | PI3 | Down-regulated in responders |
|                             | ARG1 | Down-regulated in responders |
|                             | MMP9 | Down-regulated in responders |
|                             | MGAM | Down-regulated in responders |
|                             | CA4 | Down-regulated in responders |
|                             | KAZN | Down-regulated in responders |
|                             | PGLYRP1 | Down-regulated in responders |
|                             | FCAR | Down-regulated in responders |
|                             | PROK2 | Down-regulated in responders |
|                             | MANSC1 | Down-regulated in responders |
|                             | TRPM6 | Down-regulated in responders |
|                             | SLC26A8 | Down-regulated in responders |
|                             | SULT1B1 | Down-regulated in responders |
|                             | IL1R1 | Down-regulated in responders |
|                             | MAK | Down-regulated in responders |
|                             | ADM | Down-regulated in responders |
|                             | TMEM88 | Down-regulated in responders |
### Table 3. Cont.

| Study                      | Gene  | Association Direction          |
|----------------------------|-------|--------------------------------|
| Oliver, J. et al., 2021    | CYP4F3 | Down-regulated in responders   |
|                            | REPS2  | Down-regulated in responders   |
|                            | ANXA3  | Down-regulated in responders   |
|                            | ABCA1  | Down-regulated in responders   |
|                            | F5     | Down-regulated in responders   |
|                            | ANPEP  | Down-regulated in responders   |
|                            | EPST1l | Up-regulated in responders     |
|                            | SERPING1 | Up-regulated in responders |
|                            | MS4A1  | Up-regulated in responders     |
|                            | CIQA   | Up-regulated in responders     |
|                            | BATF2  | Up-regulated in responders     |
|                            | FCRLA  | Up-regulated in responders     |
|                            | IGLL5  | Up-regulated in responders     |
|                            | MZB1   | Up-regulated in responders     |
|                            | IGJ    | Up-regulated in responders     |

### Table 4. Protein biomarkers of response to anti-TNF therapy in RA.

| Study                      | Protein Marker | Association Direction          |
|----------------------------|----------------|--------------------------------|
| Straub, R.H. et al., 2008  | Cortisol       | Down-regulated in responders   |
| Ammitzbøll, C.G. et al., 2013 | FCN1        | Down-regulated in responders   |
| Matsuyama, Y. et al., 2012 | IL33          | Down-regulated in responders   |
| Morozzi, G. et al., 2007   | COMP           | Down-regulated in responders   |
| Kohno, M. et al., 2008     | IL17 to TNF ratio | Down-regulated in responders   |
| Ortea, I. et al., 2012     | GC             | Up-regulated in non-responders |
|                            | CP             | Up-regulated in non-responders |
|                            | APOB           | Up-regulated in non-responders |
|                            | ITIH2          | Up-regulated in non-responders |
|                            | THBS1          | Up-regulated in non-responders |
|                            | C4B            | Up-regulated in non-responders |
|                            | ITIH1          | Up-regulated in non-responders |
|                            | GSN            | Up-regulated in non-responders |
|                            | APOA2          | Up-regulated in non-responders |
|                            | FN1            | Up-regulated in non-responders |
|                            | CFHR4          | Up-regulated in non-responders |
|                            | APOM           | Up-regulated in non-responders |
|                            | APMAP          | Up-regulated in non-responders |
|                            | MASP2          | Up-regulated in non-responders |
| Study                                      | Protein Marker                | Association Direction  |
|-------------------------------------------|-------------------------------|------------------------|
| Shi, R. et al., 2018 [100]                | BIRC5                         | Down-regulated in responders |
|                                           | CRP                           | Up-regulated in responders |
|                                           | IL6                           | Up-regulated in responders |
| Cañete, J.D. et al., 2011 [101]           | TNFRSF1B                      | Up-regulated in responders |
| Kayakabe, K. et al., 2012 [102]           | IL1B                          | Down-regulated in non-responders |
| Sakthiswary, R. et al., 2014 [103]        | IgA rheumatoid factor         | Up-regulated in non-responders |
| Andersen, M. et al., 2017 [104]           | MC1R                          | Down-regulated in responders |
|                                           | MC3R                          | Down-regulated in responders |
|                                           | MC5R                          | Down-regulated in responders |
|                                           | MC1R                          | Down-regulated in responders |
|                                           | MC3R                          | Down-regulated in responders |
|                                           | MC5R                          | Down-regulated in responders |
| Choi, I.Y. et al., 2015 [105]             | S100A8/S100A9 complex         | Up-regulated in responders |
| La, D.T. et al., 2008 [106]               | TNFSF13B                      | Down-regulated in responders |
| Odai, T. et al., 2009 [107]               | CX3CL1                        | Down-regulated in responders |
| Kuuliala, A. et al., 2006 [108]           | IL2                           | Down-regulated in responders |
| González-Alvaro, I. et al., 2007 [109]    | TNFSF11                       | Down-regulated in responders |
| Fabre, S. et al., 2008 [110]              | CCL2                          | Down-regulated in non-responders |
|                                           | EGF                           | Down-regulated in non-responders |
| Wijbrandts, C.A. et al., 2008 [111]       | TNF                           | Up-regulated in responders |
|                                           | CSF2                          | Up-regulated in responders |
|                                           | IL6                           | Up-regulated in responders |
|                                           | FMOD                          | Up-regulated in responders |
|                                           | CLU                           | Up-regulated in responders |
|                                           | APOE                          | Up-regulated in responders |
|                                           | HIST1H2BM                     | Up-regulated in responders |
|                                           | HSP58                         | Up-regulated in responders |
|                                           | IL1A                          | Up-regulated in responders |
|                                           | COMP                          | Up-regulated in responders |
|                                           | CAST                          | Up-regulated in responders |
|                                           | BGN                           | Up-regulated in responders |
|                                           | OGN                           | Up-regulated in responders |
|                                           | TMPRSS11A                     | Up-regulated in responders |
|                                           | IL1B                          | Up-regulated in responders |
|                                           | CCL11                         | Up-regulated in responders |
|                                           | CXCL10                        | Up-regulated in responders |
|                                           | FGF1                          | Up-regulated in responders |
|                                           | CCL2                          | Up-regulated in responders |
|                                           | IL12P70                       | Up-regulated in responders |
|                                           | IL12P40                       | Up-regulated in responders |
|                                           | IL15                          | Up-regulated in responders |
Table 4. Cont.

| Study                          | Protein Marker | Association Direction |
|-------------------------------|----------------|-----------------------|
| Lindberg, J. et al., 2010 [113]| LGALS1         | Up-regulated in responders |
|                               | SCNN1B         | Down-regulated in responders |
|                               | GMNN           | Down-regulated in responders |
|                               | PALLD          | Down-regulated in responders |
|                               | TPPP3          | Up-regulated in responders |
|                               | LGALS1         | Down-regulated in responders |
|                               | NONO           | Down-regulated in responders |
|                               | ATP5H          | Down-regulated in responders |
|                               | PGLS           | Down-regulated in responders |
|                               | UBA52          | Down-regulated in responders |
|                               | RPS12          | Down-regulated in responders |
|                               | RPLP0P6        | Down-regulated in responders |
|                               | ANAPC11        | Down-regulated in responders |
|                               | PGA3           | Up-regulated in responders |
|                               | WDR83OS        | Down-regulated in responders |
|                               | MYO15A         | Down-regulated in responders |
|                               | MRPL33         | Down-regulated in responders |
|                               | FOXC2          | Down-regulated in responders |
|                               | H3F3A          | Down-regulated in responders |
|                               | FAP            | Down-regulated in responders |
|                               | TRAF3IP2       | Down-regulated in responders |
|                               | AGPAT4         | Down-regulated in responders |
|                               | RPL36A         | Up-regulated in responders |
|                               | RIN2           | Down-regulated in responders |
|                               | RPL13A         | Down-regulated in responders |
|                               | NEK5           | Down-regulated in responders |
|                               | RPL7           | Down-regulated in responders |
| Trocmé, C. et al., 2009 [114] | APOA1          | Up-regulated in responders |
|                               | PF4            | Up-regulated in non-responders |
| Chen, D.Y. et al., 2011 [115] | IL17           | Up-regulated in non-responders |
| Meusch, U. et al., 2013 [116] | IL1R2          | Up-regulated in responders |
| Obry, A. et al., 2014 [117]   | S100A8         | Up-regulated in responders |
|                               | S100A9         | Up-regulated in responders |
| Blaschke, S. et al., 2015 [118]| Haptoglobin-α1 | Up-regulated in responders |
|                               | Haptoglobin-α2 | Up-regulated in responders |
|                               | HP             | Up-regulated in responders |
|                               | GC             | Up-regulated in responders |
|                               | APOC3          | Up-regulated in non-responders |
| Zhang, F. et al., 2015 [119]  | IL34           | Down-regulated in responders |
| Meusch, U. et al., 2015 [120]| TNFRSF1A       | Up-regulated in responders |
|                               | IL1RA          | Up-regulated in responders |
Table 4. Cont.

| Study                        | Protein Marker                        | Association Direction               |
|------------------------------|---------------------------------------|-------------------------------------|
| Obry, A. et al., 2015 [121]  | STUB1                                 | Up-regulated in responders          |
|                              | PROS1                                 | Up-regulated in responders          |
|                              | C1R                                   | Up-regulated in responders          |
|                              | CPN2                                  | Up-regulated in responders          |
|                              | CP                                    | Up-regulated in responders          |
|                              | ITIH1                                 | Up-regulated in responders          |
|                              | ITIH3                                 | Up-regulated in responders          |
|                              | DYNC1H1                               | Up-regulated in responders          |
|                              | S100A9                                | Up-regulated in responders          |
|                              | AZGP1                                 | Up-regulated in responders          |
|                              | TF                                    | Down-regulated in responders        |
|                              | PLG                                   | Up-regulated in responders          |
| Nair, S.C. et al., 2016 [122]| S100A8–S100A9 complex                 | Up-regulated in responders          |
|                              | ADAMTSL2                              | Up-regulated in non-responders      |
|                              | A2M                                   | Up-regulated in non-responders      |
|                              | APOA1                                 | Down-regulated in non-responders    |
|                              | APOA2                                 | Up-regulated in non-responders      |
|                              | APOB                                  | Up-regulated in non-responders      |
|                              | APOC1                                 | Up-regulated in non-responders      |
|                              | APOC3                                 | Up-regulated in non-responders      |
|                              | APOM                                  | Up-regulated in non-responders      |
|                              | F9                                    | Up-regulated in non-responders      |
|                              | CFL1                                  | Up-regulated in non-responders      |
|                              | C3                                    | Up-regulated in non-responders      |
|                              | C4B                                   | Up-regulated in non-responders      |
|                              | C8A                                   | Up-regulated in non-responders      |
|                              | CFHR4                                 | Down-regulated in non-responders    |
|                              | LGALS3BP                              | Up-regulated in non-responders      |
|                              | HPX                                   | Up-regulated in non-responders      |
|                              | ITIH1                                 | Up-regulated in non-responders      |
|                              | ITIH2                                 | Up-regulated in non-responders      |
|                              | TPM3                                  | Up-regulated in non-responders      |
|                              | FN1                                   | Up-regulated in non-responders      |
|                              | MASP2                                 | Up-regulated in non-responders      |
|                              | PF4                                   | Up-regulated in non-responders      |
|                              | SH3BGRHL3                             | Up-regulated in non-responders      |
|                              | ABI3BP                                | Down-regulated in non-responders    |
|                              | TCFL5                                 | Down-regulated in non-responders    |
|                              | TPM4                                  | Up-regulated in non-responders      |
|                              | TAGLN2                                | Up-regulated in non-responders      |
| Wampler Muskardin, T. et al., 2016 [124] | IFN-β–α activity ratio | Up-regulated in non-responders |
Table 4. Cont.

| Study                          | Protein Marker | Association Direction          |
|--------------------------------|----------------|--------------------------------|
| Folkersen, L. et al., 2016 [66] | ICAM1          | Down-regulated in responders   |
|                                | CXCL13         | Up-regulated in responders     |
| Nishimoto, T. et al., 2014 [68]| TRAF1          | Up-regulated in non-responders |
| Koga, T. et al., 2011 [125]     | PLAU           | Up-regulated in responders     |
|                                |                | Down-regulated in non-responders|
| Gerli, R. et al., 2008 [126]    | CD30           | Up-regulated in responders     |
| Braun-Moscovici, Y. et al., 2006 [127] | IL6        | Down-regulated in responders   |
| Nguyen, M.V.C. et al., 2018 [128] | S100A12      | Down-regulated in responders   |
|                                | TTR            | Up-regulated in responders     |
|                                | PF4            | Up-regulated in responders     |
| Otsubo, H. et al., 2018 [129]   | FOLR2          | Up-regulated in non-responders |
| Frostegård, J. et al., 2021 [130] | PCSK9         | Down-regulated in responders   |

Studies reporting biomarkers that could not be categorized as DNA, RNA or protein biomarkers are displayed below in Table 5.

Table 5. Markers which could not be categorized as DNA, RNA or protein biomarkers.

| Study                          | Marker            | Association Direction          |
|--------------------------------|-------------------|--------------------------------|
| Citro, A. et al., 2015 [131]    | CD8+ T cells      | Up-regulated in responders     |
| Hull, D.N. et al., 2016 [132]   | Th17 cells        | Up-regulated in non-responders |
| Plant, D. et al., 2016 [133]     | cg04857395        | Down-regulated in responders   |
|                                | cg26401028        | Down-regulated in responders   |
|                                | cg16426293        | Down-regulated in responders   |
|                                | cg03277049        | Down-regulated in responders   |
|                                | cg1226028         | Down-regulated in responders   |
| Talotta, R. et al., 2015 [134]  | Th17 cells        | Up-regulated in non-responders |
|                                | Th1 cells         | Up-regulated in non-responders |
| Cuppen, B.V. et al., 2016 [135] | sn1-LPC (18:3-ω3/ω6) | Down-regulated in responders |
|                                | sn1-LPC (15:0)    | Up-regulated in responders     |
|                                | ethanolamine      | Down-regulated in responders   |
|                                | lysine            | Up-regulated in responders     |
| Chara, L. et al., 2012 [136]    | CD14"highCD16"   | Up-regulated in non-responders |
|                                | CD14"lowCD16"    | Up-regulated in non-responders |
|                                | CD14"highCD16"   | Up-regulated in non-responders |
| Alzabin, S. et al., 2012 [137]  | Th17 cells        | Up-regulated in non-responders |
| Klaasen, R. et. al., 2009 [138] | lymphocyte aggregates | Up-regulated in responders     |
| Talotta, R. et al., 2016 [139]  | Macrophages       | Up-regulated in responders     |
| Priori, R. et al., 2015 [140]   | NMR spectra       | Responder/non-responder specific|

3.3. Gene Ontology Analysis Results

The DNA subset has enriched GO terms related to the definition of non-response, while the DNA gene network only expanded upon the terms NF-κB signaling and TNF-α processes.
Gene ontology analysis of DNA biomarkers revealed terms already known to be associated with anti-TNF therapy non-response in rheumatoid arthritis, namely, terms connected to the definition of non-response or anti-TNF therapy, such as inflammation, tumor necrosis factor alpha, NF-κB signaling, IL-1, IL-2, IL-6 and IL-27. A subset of the terms related to NF-κB signaling is displayed in Figure 1.

RNA biomarker subsets revealed several enriched GO terms that were not previously directly associated with anti-TNF therapy response in rheumatoid arthritis. Such enriched terms in RNA subsets include prostaglandin synthesis, response to lipopolysaccharide (LPS), interferon gamma and macrophage chemotaxis. Gene networks based on RNA biomarkers and their BIOGRID interactors revealed novel significantly enriched GO terms related to the proteasome; the term proteasome-mediated ubiquitin-dependent protein catabolic process \((p = 2.91 \times 10^{-15})\) is a significant novel hyponym. The gene ontology terms related to the proteasome and others identified in the BIOGRID RNA biomarker network are illustrated in Figure 2.

Similarly, protein subsets also revealed several enriched GO terms that were not previously directly associated with anti-TNF therapy response in rheumatoid arthritis. Gene ontology analysis revealed several enriched blood lipoprotein (HDL, VLDL and cholesterol) terms, illustrated in Figure 3.

The full results of the gene ontology subset analysis are available in Table S1. BIOGRID data gene networks based on DNA and protein biomarkers did not reveal any novel enriched GO terms but expanded the associated hyponyms of leading GO terms.

Comparative GO analysis of DNA, RNA and protein biomarkers showed no novel differences between analyzed subsets based on biomarker type. NF-κB signaling terms are specific to DNA, MHC protein complex terms are specific for RNA, while lipoprotein terms are specific to protein biomarkers.
Figure 2. Network of gene ontology term nodes related to the proteasome, as identified in RNA biomarker subsets with BIOGRID data.

Figure 3. Extended network of gene ontology term nodes related to lipids, as identified in the protein biomarker subset.

4. Discussion

The results of our study help to elucidate the mechanisms underlying response and non-response to anti-TNF therapy in rheumatoid arthritis. Biological markers linked to mechanisms associated with response and/or non-response to anti-TNF therapy have
potential clinical applications as response predictors before or during anti-TNF therapy or even as potential novel therapeutic targets.

First, there was significant enrichment of protein metabolism terms in gene network subsets based on RNA biomarkers (specifically, RNA_UP_R_DO_N_BIO). The leading GO term was the hypernym positive regulation of protein metabolic process \( (p = 3.63 \times 10^{-37}) \). Specifically, several enriched hyponyms under this leading term are associated with the proteasome, such as proteasome-mediated ubiquitin-dependent protein catabolic process \( (p = 2.91 \times 10^{-15}) \). To our best knowledge, proteasome processes have not yet been implicated in anti-TNF therapy response in rheumatoid arthritis. In RA, the autophagy and proteasome protein degradation pathways are key processes for synovial fibroblast survival [141]. In response to TNFα, the autophagy pathway, but not the proteasome, is consistently stimulated, yet there is an increased dependence on the proteasome for cell viability [141]. If autophagy is blocked in the presence of TNFα, an increase in proteasome activity occurs in some RA synovial fibroblasts but decreases in healthy synovial fibroblasts [141]. Targeting the proteasome complex thus represents a therapeutic opportunity to decrease synovial fibroblast survival, pannus growth and inflammation in RA [142–144].

Bortezomib, a proteasome inhibitor indicated for hematological cancers, was shown to decrease bone loss in an animal model of RA [145] and inflammatory cytokine production in an ex vivo study of activated T cells of healthy controls and RA patients [146]. In a recent study, delanzomib, a novel proteasome inhibitor, was successfully used together with adalimumab in a rat model of rheumatoid arthritis [147]. Moreover, two case reports showed remission of rheumatoid arthritis complicated with multiple myeloma [148] or TEMPI syndrome [149] after administration of bortezomib.

Second, several terms related to lipoproteins were found to be significantly enriched in protein biomarker subsets. In the subset containing all protein biomarkers, the leading lipoprotein terms were lipoprotein particle receptor binding \( (p = 8.81 \times 10^{-12}) \) and plasma lipoprotein particle \( (p = 4.55 \times 10^{-11}) \). Interestingly, the hyponyms very-low-density lipoprotein particle \( (p = 1.83 \times 10^{-10}) \) and spherical high-density lipoprotein particle \( (p = 5.22 \times 10^{-8}) \) suggest the role of very-low-density lipoproteins (VLDLs) and high-density lipoproteins (HDLs) in response. Comparative GO analysis showed VLDL to be specific for protein biomarkers down-regulated in responders (or up-regulated in non-responders), and HDL was shown to be up-regulated in responders (or down-regulated in non-responders). These findings confirm clinical observations of increased HDL [150,151] as well as triglyceride and total cholesterol levels [152] after anti-TNF therapy initiation. Moreover, low baseline VLDL has been linked with a better response to anti-TNF therapy [153], which coincides with our finding of VLDLs being down-regulated in responders. Although blood lipid profiles may only reflect systemic inflammation and thus also disease severity, their role in anti-TNF therapy response is not yet understood. Blood lipid profiles are potential accessible and affordable anti-TNF response biomarkers that could be integrated into clinical routine.

Third, our results show a significant enrichment of GO terms related to leukocyte chemotaxis in RNA subsets, with the leading term being negative regulation of leukocyte chemotaxis \( (p = 3.26 \times 10^{-4}) \). Hyponym investigation in a comparative analysis of RNA biomarkers up-regulated and down-regulated in responders showed the term negative regulation of macrophage chemotaxis \( (p = 3.00 \times 10^{-5}) \) to be up-regulated in responders (or down-regulated in non-responders). This finding suggests that good responders have lower macrophage infiltration than non-responders. Macrophage chemotaxis thus represents both an opportunity for response biomarker discovery as well as a therapeutic target. An example of a leukocyte chemotaxis reducing drug is montelukast, a cysteinyl leukotriene receptor antagonist used to treat asthma and allergic rhinitis. Although montelukast is mainly used to block leukotriene-dependent human airway smooth muscle contractions, it also blocks up-regulation of vascular permeability and leukocyte chemotaxis. A study has shown that montelukast decreases inflammatory cytokine production in RA and thus represents a novel therapeutic strategy [154].
Finally, our review of anti-TNF therapy response biomarkers has revealed that many response biomarkers have been reported at several levels of biological data (DNA, RNA, proteins, etc.), but only 12 biomarkers were reported by more than one study. Biomarkers reported by more than one study include the DNA biomarkers CCL4 and IL1B; the RNA biomarkers FCGR2A, FCGR3A, IL10, IL6, PTPRC and TNF; and the protein biomarkers IL6, ITIH1, S100A8 and S100A9. Recently, a Japanese cohort has demonstrated the use of interferon signatures and their dynamics for use in long-term anti-TNF drug response prediction, which validates previously reported biomarkers related to interferon proteins [155]. Interestingly, results from another recent study showed that interferon-related chemokine levels (e.g., CXCL10) correlated with disease activity but not with short-term response to anti-TNF therapy (certolizumab pegol) in a Swedish cohort [156]. These studies highlight the difficulties of biomarker replication, especially with cohorts from different ethnic backgrounds and with different study designs.

Our GO analysis of anti-TNF therapy response biomarkers highlighted several biological processes as significantly enriched in response and/or non-response to anti-TNF therapy. Our results encourage targeted analysis of these biological processes for novel biomarker discovery but also the development of novel therapeutic strategies in the treatment of RA. The highlighted therapeutic targets could be useful either as alternatives for anti-TNF therapy non-responders, as co-therapies with anti-TNF treatment or as novel maintenance strategies. Moreover, our study’s review of anti-TNF response biomarkers revealed that although response biomarkers have been extensively studied, there is a generally low rate of overlap and biomarker validation between studies.

5. Conclusions

Biological processes related to the proteasome and blood lipids could affect response to anti-TNF therapy according to gene ontology of existing anti-TNF therapy response biomarkers in RA. Our study encourages further investigation of proteasome and blood lipid processes in RA anti-TNF response.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/biomedicines10081808/s1, Table S1: Full gene ontology analysis results.

Author Contributions: Conceptualization, U.P.; data curation, G.J. and M.G.; formal Analysis, G.J.; investigation, G.J., M.G. and U.P.; methodology, G.J., M.G. and U.P.; project administration, U.P.; software, M.G.; supervision, U.P.; validation, G.J.; visualization, G.J.; writing—original draft preparation, G.J.; writing—review and editing, M.G. and U.P. All authors have read and agreed to the published version of the manuscript.

Funding: The authors acknowledge the financial support of the Slovenian Research Agency research core funding No. P3-0067 and P3-0427 and research grant No. J3-9258.

Institutional Review Board Statement: No humans or animals were involved in this study.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article or the Supplementary Materials.

Acknowledgments: The authors would like to thank Boris Gole for providing support with gene ontology software protocols.

Conflicts of Interest: The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. Cacciapaglia, F.; Venerito, V.; Stano, S.; Fornaro, M.; Lopalco, G.; Iannone, F. Comparison of Adalimumab to Other Targeted Therapies in Rheumatoid Arthritis: Results from Systematic Literature Review and Meta-Analysis. J. Pers. Med. 2022, 12, 353. [CrossRef] [PubMed]

2. Murray, K.M.; Dahl, S.L. Recombinant human tumor necrosis factor receptor (p75) Fc fusion protein (TNFR:Fc) in rheumatoid arthritis. Ann. Pharmacother. 1997, 31, 1335–1338. [CrossRef] [PubMed]
3. Scallon, B.J.; Moore, M.A.; Trinh, H.; Knight, D.M.; Ghrayeb, J. Chimeric anti-TNF-alpha monoclonal antibody cA2 binds recombinant transmembrane TNF-alpha and activates immune effector functions. *Cytokine* **1995**, *7*, 251–259. [CrossRef] [PubMed]

4. Rau, R. Adalimumab (a fully human anti-tumour necrosis factor alpha monoclonal antibody) in the treatment of active rheumatoid arthritis: The initial results of five trials. *Ann. Rheum. Dis.* **2002**, *61* (Suppl. S2), i70–i73. [CrossRef] [PubMed]

5. Choy, E.H.; Hazleman, B.; Smith, M.; Moss, K.; Lisi, L.; Scott, D.G.; Patel, J.; Sowpith, M.; Isenberg, D.A. Efficacy of a novel PEGalutyed humanized anti-TNF fragment (CDP870) in patients with rheumatoid arthritis: A phase II double-blinded, randomized, dose-escalating trial. *Rheumatology* **2002**, *41*, 1133–1137. [CrossRef]

6. Zhou, H.; Jang, H.; Fleischmann, R.M.; Bouman-Thio, E.; Xu, Z.; Marini, J.C.; Pendley, C.; Jiao, Q.; Shankar, G.; Marciniak, S.J.; et al. Pharmacokinetics and safety of golimumab, a fully human anti-TNF-alpha monoclonal antibody, in subjects with rheumatoid arthritis. *J. Clin. Pharmacol.* **2007**, *47*, 383–396. [CrossRef]

7. Zhao, S.; Nair, J.R.; Moots, R.J. Biosimilars: From Extrapolation into Off Label Use. *Curr. Pharm. Des.* **2017**, *23*, 6746–6751. [CrossRef]

8. Roda, G.; Jharap, B.; Neeraj, N.; Colombel, J.F. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin. Transl. Gastroenterol.* **2016**, *7*, e135. [CrossRef] [PubMed]

9. Shams, S.; Martinez, J.M.; Dawson, J.R.D.; Flores, J.; Gabriel, M.; Garcia, G.; Guevara, A.; Murray, K.; Pacifici, N.; Vargas, M.V.; et al. The Therapeutic Landscape of Rheumatoid Arthritis: Current State and Future Directions. *Front. Pharmacol.* **2021**, *12*, 680043. [CrossRef] [PubMed]

10. Cohen, S.B.; Emery, P.; Greenwald, M.W.; Dougadoos, M.; Furie, R.A.; Genovese, M.C.; Keystone, E.C.; Loveless, J.E.; Burmester, G.R.; Cravets, M.W.; et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheumatol.* **2006**, *54*, 2793–2806. [CrossRef] [PubMed]

11. Emery, P.; Fleischmann, R.; Filipowicz-Sosnowska, A.; Schechtman, J.; Szczepanski, L.; Kavanaugh, A.; Racewicz, A.J.; van Vollenhoven, R.F.; Li, N.F.; Agarwal, S.; et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase III randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheumatol.* **2006**, *54*, 1390–1400. [CrossRef] [PubMed]

12. Fraenkel, L.; Bathon, J.M.; England, B.R.; St Clair, E.W.; Arayssi, T.; Carandang, K.; Deane, K.D.; Genovese, M.; Huston, K.K.; Kerr, G.; et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol.* **2021**, *73*, 1108–1123. [CrossRef]

13. Stark, C.; Breitkreutz, B.J.; Reguly, T.; Boucher, L.; Breitkreutz, A.; Tyers, M. BioGRID: A general repository for interaction datasets. *Nucleic Acids Res.* **2006**, *34*, D535–D539. [CrossRef]

14. Oughtred, R.; Stark, C.; Breitkreutz, B.J.; Rust, J.; Boucher, L.; Chang, C.; Kolas, N.; O'Donnell, L.; Leung, G.; McAdam, R.; et al. The BioGRID interaction database: 2019 update. *Nucleic Acids Res.* **2019**, *47*, D529–D541. [CrossRef] [PubMed]

15. Coutin, N. Biogridr: BioGRID R API. 2015. Available online: https://github.com/npjc/biogridr (accessed on 17 January 2021).

16. R Core Team. R: A Language and Environment for Statistical Computing. 2020. Available online: https://cran.r-project.org/ (accessed on 13 September 2021).

17. Shannon, P.; Markiel, A.; Ozier, O.; Baliga, N.S.; Wang, J.T.; Ramage, D.; Amin, N.; Schwikowski, B.; Ideker, T. Cytoscape: A software environment for integrated models of biomolecular interaction networks. *Genome Res.* **2003**, *13*, 2498–2504. [CrossRef] [PubMed]

18. Bindea, G.; Mlecnik, B.; Hackl, H.; Charoentong, P.; Tosolini, M.; Kirilovsky, A.; Fridman, W.H.; Pagès, F.; Trajanoski, Z.; Galon, J. ClueGo: A Cytoscape plug-in to decipher functionally grouped gene ontology and pathway annotation networks. *Bioinformatics* **2009**, *25*, 1091–1093. [CrossRef] [PubMed]

19. Raudvere, U.; Kolberg, L.; Kuzmin, I.; Arak, T.; Adler, P.; Peterson, H.; Vilo, J. g:Profiler: A web server for functional enrichment analysis and conversions of gene lists (2019 update). *Nucleic Acids Res.* **2019**, *47*, W191–W198. [CrossRef]

20. Criswell, L.A.; Lum, R.F.; Turner, K.N.; Woehl, B.; Zhu, Y.; Wang, J.; Tiwari, H.K.; Edberg, J.C.; Kimberly, R.P.; Moreland, L.W.; et al. The influence of genetic variation in the HLA-DRB1 and LTA-TNF regions on the response to treatment of early rheumatoid arthritis with methotrexate or etanercept. *Arthritis Rheum.* **2004**, *50*, 2750–2756. [CrossRef] [PubMed]

21. Lee, Y.H.; Rho, Y.H.; Choi, S.J.; Ji, J.D.; Song, G.G. Association of TNF-alpha -308 G/A polymorphism with responsiveness to TNF-alpha-blockers in rheumatoid arthritis: A meta-analysis. *Rheumatol. Int.* **2006**, *25*, 157–161. [CrossRef] [PubMed]

22. Ongaro, A.; De Mattei, M.; Pellati, A.; Caruso, A.; Ferretti, S.; Masieri, F.F.; Fotinidi, M.; Farina, I.; Trotta, F.; Padovan, M. Can tumor necrosis factor receptor II gene 676T>G polymorphism predict the response grading to anti-TNFalpha therapy in rheumatoid arthritis? *Rheumatol. Int.* **2008**, *28*, 901–908. [CrossRef]

23. Jančič, I.; Arsenović-Rainin, N.; Sefik-Buklica, M.; Živovinović, S.; Damjanov, N.; Spasovski, V.; Srsenčić, S.; Stanković, B.; Pavlović, S. -174G/C interleukin-6 gene promoter polymorphism predicts therapeutic response to etanercept in rheumatoid arthritis. *Rheumatol. Int.* **2013**, *33*, 1481–1486. [CrossRef]

24. Lee, Y.H.; Bae, S.C.; Song, G.G. Functional FCGR3A 158 V/F and IL-6 -174 C/G polymorphisms predict response to biologic therapy in patients with rheumatoid arthritis: A meta-analysis. *Rheumatol. Int.* **2014**, *34*, 1409–1415. [CrossRef] [PubMed]

25. Lee, Y.H.; Bae, S.C. Associations between PTPRC rs10919563 A/G and FCGR2A R131H polymorphisms and responsiveness to TNF blockers in rheumatoid arthritis: A meta-analysis. *Rheumatol. Int.* **2016**, *36*, 837–844. [CrossRef] [PubMed]
26. Schotte, H.; Schmidt, H.; Gaubitz, M.; Drysda, S.; Kekow, J.; Willeke, P.; Schlüter, B. Interleukin-6 promoter haplotypes are associated with etanercept response in patients with rheumatoid arthritis. *Clin. Rheumatol.* 2015, 34, 2021–2028. [CrossRef] [PubMed]

27. Pappas, D.A.; Oh, C.; Plenge, R.M.; Kremer, J.M.; Greenberg, J.D. Association of rheumatoid arthritis risk alleles with response to anti-TNF biology: Results from the CORRONA registry and meta-analysis. *Inflammation* 2013, 36, 279–284. [CrossRef] [PubMed]

28. Morales-Lara, M.J.; Cañete, J.D.; Torres-Moreno, D.; Hernández, M.V.; Pedroso, F.; Celis, R.; García-Simón, M.S.; Conesa-Zamora, P. Effects of polymorphisms in TRAILR1 and TNFR1A on the response to anti-TNF therapies in patients with rheumatoid and psoriatic arthritis. *J. Bone Spine* 2012, 79, 591–596. [CrossRef]

29. Pers, Y.M.; Cadart, D.; Kitzel, C.; Ravel, P.; Düven, V.; Fabre, S.; Jorgensen, C.; Toutou, I. TNFRII polymorphism is associated with response to TNF blockers in rheumatoid arthritis patients seronegative for ACPA. *J. Bone Spine* 2014, 81, 370–372. [CrossRef] [PubMed]

30. Iwaszko, M.; Święrkot, J.; Kolossa, K.; Jeka, S.; Wiland, P.; Bogunia-Kubik, K. Influence of CD94 and NKG2A variants on susceptibility to rheumatoid arthritis and efficacy of anti-TNF treatment. *J. Bone Spine* 2016, 83, 75–79. [CrossRef] [PubMed]

31. O’Rielly, D.D.; Roslin, N.M.; Beyene, J.; Pope, A.; Rahman, P. TNF-alpha-308 G/A polymorphism and responsiveness to TNF-alpha blocker treatment in moderate to severe rheumatoid arthritis: A systematic review and meta-analysis. *Pharm. J.* 2009, 9, 161–167. [CrossRef]

32. Ferreiro-Iglesias, A.; Montes, A.; Perez-Pampin, E.; Cañete, J.D.; Raya, E.; Magro-Checa, C.; Vasiropoulos, Y.; Sarafidou, T.; Caliz, R.; Ferrer, M.A.; et al. Replication of PTPRC as genetic biomarker of response to TNF inhibitors in patients with rheumatoid arthritis. *Pharm. J.* 2016, 16, 137–140. [CrossRef]

33. Julià, A.; Fernandez-Nebro, A.; Blanco, F.; Ortiz, A.; Cañete, J.D.; Maymó, J.; Alperi-López, M.; Fernández-Gutierrez, B.; Olivé, A.; Corominas, H.; et al. A genome-wide association study identifies a new locus associated with the response to anti-TNF therapy in rheumatoid arthritis. *Pharm. J.* 2016, 16, 147–150. [CrossRef] [PubMed]

34. Kang, C.P.; Lee, K.W.; Yoo, D.H.; Kang, C.; Bae, S.C. The influence of a polymorphism at position -857 of the tumour necrosis factor alpha gene on clinical response to etanercept therapy in rheumatoid arthritis. *Rheumatology* 2005, 44, 547–552. [CrossRef] [PubMed]

35. Seitz, M.; Wirthmüller, U.; Möller, B.; Villiger, P.M. The -308 tumour necrosis factor-alpha gene polymorphism predicts therapeutic response to TNFalpha-blockers in rheumatoid arthritis and spondyloarthritis patients. *Rheumatology* 2007, 46, 93–96. [CrossRef] [PubMed]

36. Iannaccone, C.K.; Lee, Y.C.; Cui, J.; Frits, M.L.; Glass, R.J.; Plenge, R.M.; Solomon, D.H.; Weinblatt, M.E.; Shadick, N.A. Using genetic and clinical data to understand response to disease-modifying anti-rheumatic drug therapy: Data from the Brigham and Women’s Hospital Rheumatoid Arthritis Study. *Rheumatology* 2011, 50, 40–46. [CrossRef]

37. Dávila-Fajardo, C.L.; Márquez, A.; Pascual-Salcedo, D.; Moreno Ramos, M.J.; Garcia-Portales, R.; Magro, C.; Alegre-Sancho, J.J.; Balsa, A.; Cabeza-Barrera, J.; Raya, E.; et al. Confirmation of -174G/C interleukin-6 gene promoter polymorphism as a genetic marker predicting antitumor necrosis factor treatment outcome. *Pharm. Genom.* 2014, 24, 1–5. [CrossRef] [PubMed]

38. Montes, A.; Perez-Pampin, E.; Narváez, J.; Cañete, J.D.; Navarro-Sarabia, F.; Moreira, V.; Fernández-Nebro, A.; Del Carmen Ordóñez, M.; de la Serna, A.R.; Magallares, B.; et al. Association of FCGR2A with the response to infliximab treatment of patients with rheumatoid arthritis. *Pharm. Genom.* 2014, 24, 238–245. [CrossRef] [PubMed]

39. Bowes, J.D.; Potter, C.; Gibbons, L.J.; Hyrich, K.; Plant, D.; Morgan, A.W.; Wilson, A.G.; Isaacs, J.D.; Worthington, J.; Barton, A.; et al. Investigation of genetic variants within candidate genes of the TNFRSF1B signalling pathway on the response to anti-TNF agents in a UK cohort of rheumatoid arthritis patients. *Pharm. Genom.* 2014, 24, 1791–1792. [CrossRef] [PubMed]

40. Miceli-Richard, C.; Comets, E.; Verstuyft, C.; Tamouza, R.; Loiseau, P.; Ravaud, P.; Kupper, H.; Becquemont, L.; Charron, D.; Mariette, X. A single tumour necrosis factor haplotype influences the response to adalimumab in rheumatoid arthritis. *Ann. Rheum. Dis.* 2008, 67, 478–484. [CrossRef]

41. Tsukahara, S.; Ikari, K.; Sato, E.; Yamanaka, H.; Hara, M.; Tomatsu, T.; Momohara, S.; Kamatani, N. A polymorphism in the gene encoding the Fcgamma IIIA receptor is a possible genetic marker to predict the primary response to infliximab in Japanese patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 2008, 67, 1791–1792. [CrossRef]

42. Cañete, J.D.; Suárez, B.; Hernández, M.V.; Sanmartí, R.; Regó, I.; Celis, R.; Moll, C.; Pinto, J.A.; Blanco, F.J.; Lozano, F. Influence of variants of Fc gamma receptors IIa and IIIA on the American College of Rheumatology and European League Against Rheumatism responses to anti-tumour necrosis factor alpha therapy in rheumatoid arthritis. *Ann. Rheum. Dis.* 2009, 68, 1547–1552. [CrossRef] [PubMed]

43. Potter, C.; Cordell, H.J.; Barton, A.; Daly, A.K.; Hyrich, K.L.; Mann, D.A.; Morgan, A.W.; Wilson, A.G.; Isaacs, J.D.; Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate. Association between anti-tumour necrosis factor treatment response and genetic variants within the TLR and NF{kappa}B signalling pathways. *Ann. Rheum. Dis.* 2010, 69, 1315–1320. [CrossRef]

44. Coulthard, L.R.; Taylor, J.C.; Eyre, S.; Robinson, J.I.; Wilson, A.G.; Isaacs, J.D.; Hyrich, K.; Emery, P.; Barton, A.; Barrett, J.H.; et al. Genetic variants within the MAP kinase signalling network and anti-TNF treatment response in rheumatoid arthritis patients. *Ann. Rheum. Dis.* 2011, 70, 98–103. [CrossRef]
45. Acosta-Colman, J.; Palau, N.; Tornerio, J.; Fernández-Nebro, A.; Blanco, F.; González-Alvaro, I.; Cañete, J.D.; Maymó, J.; Ballina, J.; Fernández-Gutiérrez, B.; et al. GWAS replication study confirms the association of PDE3A-SLCO1C1 with anti-TNF therapy response in rheumatoid arthritis. *Pharmacogenomics* 2013, **14**, 727–734. [CrossRef] [PubMed]

46. Dávila-Fajardo, C.L.; van der Straaten, T.; Baak-Pablo, R.; Medarde Caballero, C.; Cabeza Barrera, J.; Huizinga, T.W.; Guchelaar, H.J.; Swen, J.J. FcGR genetic polymorphisms and the response to adalimumab in patients with rheumatoid arthritis. *Pharmacogenomics* 2015, **16**, 373–381. [CrossRef] [PubMed]

47. Sun, Y.; Mo, L.; Feng, X.; Yang, D.; Tan, T.; Zeng, L.; Hui, L.; Wang, Y.; Liu, C.; He, L. Association of Fcgamma receptor type 2A and 3A genotypes with rheumatoid arthritis in Chinese population. *Pharmacogenomics* 2017, **18**, 255–264. [CrossRef]

48. Morales-Lara, M.J.; Conesa-Zamora, P.; Garcia-Simon, M.S.; Pedroso, F.; Santacilara, V.; Perez-Guijermo, M.; Soriani-Navarro, E. Association between the FCGR3A V158F polymorphism and the clinical response to infliximab in rheumatoid arthritis and spondyloarthritis patients. *Scand. J. Rheumatol.* 2010, **39**, 518–520. [CrossRef] [PubMed]

49. Lee, Y.H.; Ji, J.D.; Bae, S.C.; Song, G.G. Associations between tumor necrosis factor-alpha (TNF-alpha) -308 and -238 G/A polymorphisms and shared epitope status and responsiveness to TNF-alpha blockers in rheumatoid arthritis: A metaanalysis update. *J. Rheumatol.* 2010, **37**, 740–746. [CrossRef] [PubMed]

50. Liu, C.; Batliwalla, F.; Li, W.; Lee, A.; Roubenoff, R.; Beckman, E.; Khalili, H.; Damle, A.; Kern, M.; Furie, R.; et al. Genome-wide association scan identifies candidate polymorphisms associated with differential response to anti-TNF treatment in rheumatoid arthritis. *Med. Gen. 2008, **14**, 575–581. [CrossRef] [PubMed]

51. Tan, R.J.; Gibbons, L.J.; Potter, C.; Hyrich, K.L.; Morgan, A.W.; Wilson, A.G.; Isaacs, J.D.; Barton, A. Investigation of rheumatoid arthritis susceptibility genes identifies association of AFF3 and CD226 variants with response to anti-tumour necrosis factor treatment. *Ann. Rheum. Dis.* 2010, **69**, 1029–1035. [CrossRef] [PubMed]

52. Plant, D.; Bowes, J.; Potter, C.; Hyrich, K.L.; Morgan, A.W.; Wilson, A.G.; Isaacs, J.D.; Barton, A.; Wellcome Trust Case Control Consortium; British Society for Rheumatology Biologics Register; et al. Genome-wide association study of genetic predictors of anti-tumor necrosis factor treatment efficacy in rheumatoid arthritis identifies associations with polymorphisms at seven loci. *Arthritis Rheumatol.* 2011, **63**, 643–653. [CrossRef] [PubMed]

53. McGeough, C.M.; Berrad, D.; Wright, G.; Mathews, C.; Cunningham, R.T.; Bjourson, A.J. Killer immunoglobulin-like receptor and human leukocyte antigen-C genotypes in rheumatoid arthritis primary responders and non-responders to anti-TNF-α therapy. *Rheumatol. Int.* 2012, **32**, 1647–1653. [CrossRef] [PubMed]

54. Krintel, S.B.; Essioux, L.; Wool, A.; Johansen, J.S.; Schreiber, E.; Zekharya, T.; Akiva, P.; Ostergaard, M.; Hetland, M.L. CD6 and syntaxin binding protein 6 variants and response to tumor necrosis factor alpha inhibitors in Danish patients with rheumatoid arthritis. *PLoS ONE* 2012, **7**, e38539. [CrossRef] [PubMed]

55. Plant, D.; Prajapati, R.; Hyrich, K.L.; Morgan, A.W.; Wilson, A.G.; Isaacs, J.D.; Barton, A.; Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate. Replication of association of the PTPRC gene with response to anti-tumor necrosis factor therapy in a large UK cohort. *Arthritis Rheum.* 2012, **64**, 665–670. [CrossRef] [PubMed]

56. Cui, J.; Stahl, E.A.; Saevardsdottir, S.; Miceli, C.; Diogo, D.; Trynka, G.; Raj, T.; Mirkov, M.U.; Canhao, H.; Ikari, K.; et al. Genome-wide association study and gene expression analysis identifies CD84 as a predictor of response to etanercept therapy in rheumatoid arthritis. *PLoS Genet.* 2013, **9**, e1003394. [CrossRef] [PubMed]

57. Cui, J.; Saevardsdottir, S.; Thomson, B.; Padyukov, L.; van der Helm-van Mil, A.H.; Nitiitham, J.; Hughes, L.B.; de Vries, N.; Raychaudhuri, S.; Alfredsson, L.; et al. Rheumatoid arthritis risk allele PTPRC is also associated with response to anti-tumor necrosis factor alpha therapy. *Arthritis Rheum.* 2010, **62**, 1849–1861. [CrossRef] [PubMed]

58. Sode, J.; Vogel, U.; Bank, S.; Andersen, P.S.; Thomsen, M.K.; Hetland, M.L.; Locht, H.; Heegaard, N.H.; Andersen, V. Anti-TNF treatment response in rheumatoid arthritis patients is associated with genetic variation in the NLRP3-inflammasome. *PLoS ONE* 2014, **9**, e100361. [CrossRef]

59. Umicevic Mirkov, M.; Cui, J.; Vermeulen, S.H.; Stahl, E.A.; Toonen, E.J.; Makkinje, R.R.; Lee, A.T.; Huizinga, T.W.; Allaart, R.; Barton, A.; et al. Genome-wide association analysis of anti-TNF drug response in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 2013, **72**, 1375–1381. [CrossRef]

60. Canhão, H.; Rodrigues, A.M.; Santos, M.J.; Carmona-Fernandes, D.; Bettencourt, B.F.; Cui, J.; Rocha, F.L.; Canas Silva, J.; Polido-Pereira, J.; Pereira Silva, J.A.; et al. TRAF1/C5 but not PTPRC variants are potential predictors of rheumatoid arthritis primary responders to anti-tumor necrosis factor treatment. *Biomed Res. Int.* 2015, **2015**, 490295. [CrossRef]

61. Avila-Pedretti, G.; Tornero, J.; Fernández-Nebro, A.; Blanco, F.; Gonzalez-Alvaro, I.; Cañete, J.D.; Maymó, J.; Alperiz, M.; Fernández-Gutiérrez, B.; Olivé, A.; et al. Variation at FCGR2A and functionally related genes is associated with the response to anti-TNF therapy in rheumatoid arthritis. *PLoS ONE* 2015, **10**, e0122088. [CrossRef] [PubMed]

62. Schotte, H.; Schlüter, B.; Schmid, H.; Gaußitz, M.; Drynda, S.; Kekow, J.; Willeke, P. Putative IL-10 Low Producer Genotypes Are Associated with a Favourable Etanercept Response in Patients with Rheumatoid Arthritis. *PLoS ONE* 2015, **10**, e0130907. [CrossRef]

63. Sode, J.; Vogel, U.; Bank, S.; Andersen, P.S.; Hetland, M.L.; Locht, H.; Heegaard, N.H.; Andersen, V. Genetic Variations in Pattern Recognition Receptor Loci Are Associated with Anti-TNF Response in Patients with Rheumatoid Arthritis. *PLoS ONE* 2015, **10**, e0139781. [CrossRef]
64. Honke, K.; Hallgrímsdóttir, I.; Wu, C.; Sebro, R.; Jewell, N.P.; Sakurai, T.; Iwamoto, M.; Minota, S.; Jawahere, D. A longitudinal genome-wide association study of anti-tumor necrosis factor response among Japanese patients with rheumatoid arthritis. *Arthritis Res. Ther.* 2016, 18, 12. [CrossRef] [PubMed]

65. Jančić, I.; Šefik-Bukilica, M.; Živojinović, S.; Damjanov, N.; Spasovski, V.; Kotur, N.; Klassen, K.; Pavlović, S.; Bufan, B.; Arsenović-Ranin, N. Influence of Promoter Polymorphisms of the TNF-α (-308G/A) and IL-6 (-174G/C) Genes on Therapeutic Response to Etanercept in Rheumatoid Arthritis. *J. Med. Biochem.* 2015, 34, 414–421. [CrossRef]

66. Folkersen, L.; Brynedal, B.; Diaz-Gallo, L.M.; Ramsköld, D.; Shchetsynsky, K.; Westerlind, H.; Sundström, Y.; Schepis, D.; Hensvold, A.; Vivar, N.; et al. Integration of known DNA, RNA and protein biomarkers provides prediction of anti-TNF response in rheumatoid arthritis: Results from the COMBINE study. *Mol. Med.* 2016, 22, 322–328. [CrossRef]

67. Gębura, K.; Świerkot, J.; Wysoczarska, B.; Korman, L.; Nowak, B.; Wiland, P.; Bogunia-Kubik, K. Polymorphisms within Genes Involved in Regulation of the NF-kB Pathway in Patients with Rheumatoid Arthritis. *Int. J. Mol. Sci.* 2017, 18, 1432. [CrossRef] [PubMed]

68. Nishimoto, T.; Setza, N.; Anan, R.; Yamamoto, T.; Kaneko, Y.; Takeuchi, T.; Kuwana, M. A single nucleotide polymorphism of TRAF1 predicts the clinical response to anti-TNF treatment in Japanese patients with rheumatoid arthritis. *Clin. Exp. Rheumatol.* 2014, 32, 211–217. [PubMed]

69. Sarsour, K.; Greenberg, J.; Johnston, J.A.; Nelson, D.R.; O’Brien, L.A.; Oddoux, C.; Ostrer, H.; Pearlman, A.; Reed, G. The role of the FcGRllla polymorphism in modifying the association between treatment and outcome in patients with rheumatoid arthritis treated with rituximab versus TNF-α antagonist therapies. *Clin. Exp. Rheumatol.* 2013, 31, 189–194. [PubMed]

70. Vasiliopoulos, Y.; Bagiatis, V.; Stamatopoulou, D.; Zisopoulou, D.; Alexiou, I.; Sarafidou, T.; Settas, L.; Sakkas, L.; Mamouris, Z. Association of anti-CCP positivity and carriage of TNFRII susceptibility variant with anti-TNF-α response in rheumatoid arthritis. *Clin. Exp. Rheumatol.* 2011, 29, 701–704. [PubMed]

71. Rooryck, C.; Barnetche, T.; Richez, C.; Laleye, A.; Arveiler, B.; Schaeverbeke, T. Influence of FCGRA3A-V212F and TNFRSF1B-264A polymorphisms on the C-reactive protein response to anti-TNF-alpha therapy and clinical disease progression in Rheumatoid Arthritis. *Ann. Rheum. Dis.* 2019, 78, 1055–1061. [CrossRef] [PubMed]

72. Cuchacovich, M.; Soto, L.; Edwardes, M.; Gutierrez, M.; Llanos, C.; Pacheco, D.; Sabugo, F.; Alamo, M.; Fuentelaba, C.; Villanueva, L.; et al. Tumour necrosis factor (TNF)alpha -308 G/G promoter polymorphism and TNFalpha levels correlate with a better response to adalimumab in patients with rheumatoid arthritis. *Scand. J. Rheumatol.* 2006, 35, 435–440. [CrossRef]

73. Tutuncu, Z.; Kavanaugh, A.; Zvaifler, N.; Corr, M.; Deutsch, R.; Boyle, D. Fcgamma receptor type IIIA polymorphisms influence treatment outcomes in patients with inflammatory arthritis treated with tumor necrosis factor alpha-blocking agents. *Arthritis Rheum.* 2005, 52, 2693–2696. [CrossRef] [PubMed]

74. Sode, J.; Vogel, U.; Bank, S.; Andersen, P.S.; Hetland, M.L.; Locht, H.; Heegaard, N.H.H.; Andersen, V. Confirmation of an IRAK3 polymorphism as a genetic marker predicting response to anti-TNF treatment in rheumatoid arthritis. *Pharm. J.* 2018, 18, 81–86. [CrossRef] [PubMed]

75. Iwaszko, M.; Świerkot, J.; Kolossa, K.; Jeka, S.; Wiland, P.; Bogunia-Kubik, K. Influence of NKG2D Genetic Variants on Response to Anti-TNF Agents in Patients with Rheumatoid Arthritis. *Genes* 2018, 9, 64. [CrossRef]

76. Skapenko, A.; Smolen, J.S.; Kavanaugh, A.; Arora, V.; Kupper, H.; Schulze-Koops, H.; Arce, V.; et al. TNF-α association with clinical and radiographic response in adalimumab plus methotrexate- or adalimumab- plus methotrexate-treated rheumatoid arthritis patients in OPTIMA. *Clin. Exp. Rheumatol.* 2019, 37, 783–790. [PubMed]

77. Spiliopoulos, A.; Colombo, M.; Plant, D.; Nair, N.; Cui, J.; Coenen, M.J.; Ikari, K.; Yamanaka, H.; Saevardsdottir, S.; Padyukov, L.; et al. Association of response to TNF inhibitors in rheumatoid arthritis with quantitative trait loci for. *Ann. Rheum. Dis.* 2019, 78, 1055–1061. [CrossRef] [PubMed]

78. Wielińska, J.; Kolossa, K.; Świerkot, J.; Dratwa, M.; Iwaszko, M.; Bugaj, B.; Wysoczarska, B.; Chaszczewska-Markowska, M.; Jeka, S.; Bogunia-Kubik, K. Polymorphisms within the RANK and RANKL Encoding Genes in Patients with Rheumatoid Arthritis: Association with Disease Progression and Effectiveness of the Biological Treatment. *Arch Immunol. Ther. Exp.* 2020, 68, 24. [CrossRef]

79. Gibson, D.S.; McGeough, C.M.; Watterson, S.; Blayney, J.; Wright, G.D.; Pendleton, A.; Gardiner, P.; Small, D.; Eakin, A.J.; Ahmed, T.; et al. Anti-tumour necrosis factor-alpha response associated with combined CD226 and HLA-DRB1[*]0404 haplotype in rheumatoid arthritis. *Clin. Exp. Rheumatol.* 2013, 31, 385–392. [CrossRef]

80. Iwaszko, M.; Wielińska, J.; Świerkot, J.; Kolossa, K.; Sokolik, B.; Bugaj, B.; Chaszczewska-Markowska, M.; Jeka, S.; Bogunia-Kubik, K. Gene Polymorphisms as Potential Biomarkers of Disease Susceptibility and Response to TNF Inhibitors in Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Patients. *Front. Immunol.* 2021, 12, 631603. [CrossRef]

81. Stuhlmüller, B.; Häupl, T.; Hernandez, M.M.; Grützkau, A.; Kuban, R.J.; Tandon, N.; Voss, J.W.; Salfeld, J.; Kinne, R.W.; Burmester, G.R. CD11c as a transcriptional biomarker to predict response to anti-TNF therapy with adalimumab in patients with rheumatoid arthritis. *Clin. Pharmacol. Ther.* 2010, 87, 311–321. [CrossRef] [PubMed]

82. Sekiguchi, N.; Kawauuchi, S.; Furuya, T.; Inaba, N.; Matsuda, K.; Ando, S.; Ogawara, M.; Aburatani, H.; Kameda, H.; Amano, K.; et al. Messenger ribonucleic acid expression profile in peripheral blood cells from RA patients following treatment with an anti-TNF-alpha monoclonal antibody, infliximab. *Rheumatology* 2008, 47, 780–788. [CrossRef] [PubMed]

83. Wright, H.L.; Thomas, H.B.; Moots, R.J.; Edwards, S.W. Interferon gene expression signature in rheumatoid arthritis neutrophils correlates with a good response to TNFi therapy. *Rheumatology* 2015, 54, 188–193. [CrossRef] [PubMed]
84. Wright, H.L.; Cox, T.; Moots, R.J.; Edwards, S.W. Neutrophil biomarkers predict response to therapy with tumor necrosis factor inhibitors in rheumatoid arthritis. *J. Leukoc. Biol.* 2016, 101, 785–795. [CrossRef] [PubMed]

85. Tsuzaka, K.; Iiemi, Y.; Takeuchi, T.; Shinozaki, N.; Morishita, T. ADAMTS5 is a biomarker for prediction of response to infliximab in patients with rheumatoid arthritis. *J. Rheumatol.* 2010, 37, 1454–1460. [CrossRef] [PubMed]

86. Oliveira, R.D.; Fontana, V.; Junta, C.M.; Marques, M.M.; Macedo, C.; Rassi, D.M.; Passos, G.A.; Donadi, E.A.; Louzada-Junior, P. Differential gene expression profiles may differentiate responder and nonresponder patients with rheumatoid arthritis for methotrexate (MTX) monotherapy and MTX plus tumor necrosis factor inhibitor combined therapy. *J. Rheumatol.* 2012, 39, 1524–1532. [CrossRef] [PubMed]

87. Lequerré, T.; Gauthier-Jauneau, A.C.; Bansard, C.; Derambure, C.; Hiron, M.; Vittecoq, O.; Daveau, M.; Mejjad, O.; Daragon, A.; Tron, F.; et al. Gene profiling in white blood cells predicts infliximab responsiveness in rheumatoid arthritis. *Arthritis Res. Ther.* 2006, 8, R105. [CrossRef]

88. Koczan, D.; Drynda, S.; Hecker, M.; Drynda, A.; Guthke, R.; Kekow, J.; Thiessen, H.J. Molecular discrimination of responders and nonresponders to anti-TNF alpha therapy in rheumatoid arthritis by etanercept. *Arthritis Res. Ther.* 2008, 10, R50. [CrossRef]

89. van Baarsen, L.G.; Wijbrands, C.A.; Rustenburg, F.; Cantaert, T.; van der Puij Kraan, T.C.; Baeten, D.L.; Dijkmans, B.A.; Tak, P.P.; Verweij, C.L. Regulation of IFN gamma response gene activity during infliximab treatment in rheumatoid arthritis is associated with clinical response to treatment. *Arthritis Res. Ther.* 2010, 12, R11. [CrossRef] [PubMed]

90. Toonen, E.J.; Gillissen, C.; Franke, B.; Kievit, W.; Eijsbouts, A.M.; den Broeder, A.A.; van Reijmersdal, S.V.; Veltman, J.A.; Scheffer, H.; Radstake, T.R.; et al. Validation study of existing gene expression signatures for anti-TNF-α treatment in patients with rheumatoid arthritis. *PLoS ONE* 2012, 7, e33199. [CrossRef]

91. Thomson, T.M.; Lescarbeau, R.M.; Drubin, D.A.; Lafflein, D.; de Graaf, D.; Fryburg, D.A.; Littman, B.; Deehan, R.; Van Hooser, A. Blood-based identification of non-responders to anti-TNF therapy in rheumatoid arthritis. *BMC Med. Genom.* 2015, 8, 26. [CrossRef] [PubMed]

92. Poliska, S.; Besenyei, T.; Végó, E.; Hamar, A.; Pusztai, A.; Vánsca, A.; Bodnár, N.; Szamosi, S.; Csumita, M.; Kerekes, G.; et al. Gene expression analysis of vascular pathophysiology related to anti-TNF treatment in rheumatoid arthritis. *Arthritis Res. Ther.* 2019, 21, 94. [CrossRef]

93. Oliver, J.; Nair, N.; Orozco, G.; Smith, S.; Hyrich, K.L.; Morgan, A.; Isaacs, J.; Wilson, A.G.; Barton, A.; Plant, D.; et al. Transcriptome-wide study of TNF-inhibitor therapy in rheumatoid arthritis reveals early signature of successful treatment. *Arthritis Res. Ther.* 2021, 23, 80. [CrossRef] [PubMed]

94. Straub, R.H.; Pongratz, G.; Cutolo, M.; Wijbrands, C.A.; Baeten, D.; Fleck, M.; Atzeni, F.; Grunke, M.; Kalden, J.R.; Schölermich, J.; et al. Increased cortisol relative to adrenocorticotropic hormone predicts improvement during anti-tumor necrosis factor therapy in rheumatoid arthritis. *Arthritis Rheumatol.* 2008, 58, 976–984. [CrossRef]

95. Ammitzbøll, C.G.; Thiel, S.; Jenseniuss, J.C.; Ellingsen, T.; Hørslev-Petersen, K.; Hetland, M.L.; Junker, P.; Krogh, N.S.; Østergaard, M.; Stengaard-Pedersen, K. M-ficolin levels reflect disease activity and predict remission in early rheumatoid arthritis. *Arthritis Rheumatol.* 2013, 65, 3045–3050. [CrossRef] [PubMed]

96. Matsuyama, Y.; Okazaki, H.; Hoshino, M.; Onishi, S.; Kamata, Y.; Nagatani, K.; Nagashima, T.; Iwamoto, M.; Yoshio, T.; Ohto-Ozaki, H.; et al. Sustained elevation of interleukin-33 in sera and synovial fluids from patients with rheumatoid arthritis non-responsive to anti-tumor necrosis factor: Possible association with persistent IL-1β signaling and a poor clinical response. *Rheumatol. Int.* 2012, 32, 1397–1401. [CrossRef]

97. Morozzi, G.; Fabbroni, M.; Bellissi, F.; Cucini, S.; Simpatico, A.; Galeazzi, M. Low serum level of COMP, a cartilage turnover receptor gene expression in stimulated whole blood cultures is useful to predict response to anti-TNF therapies in rheumatoid arthritis. *Int. J. Rheum. Dis.* 2014, 17, 872–877. [CrossRef] [PubMed]

98. Kohno, M.; Tsutsumi, A.; Matsui, H.; Sugihara, M.; Suzuki, T.; Mamura, M.; Goto, D.; Matsumoto, I.; Ito, S.; Suguro, T.; et al. Interleukin-17 gene expression in patients with rheumatoid arthritis. *Mod. Rheumatol.* 2018, 28, 126–132. [CrossRef] [PubMed]

99. Kohno, M.; Tsutsumi, A.; Matsui, H.; Sugihara, M.; Suzuki, T.; Mamura, M.; Goto, D.; Matsumoto, I.; Ito, S.; Suguro, T.; et al. Interleukin-17 gene expression in patients with rheumatoid arthritis. *Mod. Rheumatol.* 2018, 28, 152–155. [CrossRef] [PubMed]

100. Orteza, I.; Roschitzki, B.; Ovalles, J.G.; Hoshino, M.; Onishi, S.; Kamata, Y.; Nagatani, K.; Nagashima, T.; Iwamoto, M.; Yoshio, T.; Ohto-Ozaki, H.; et al. Sustained elevation of interleukin-33 in sera and synovial fluids from patients with rheumatoid arthritis non-responsive to anti-tumor necrosis factor: Possible association with persistent IL-1β signaling and a poor clinical response. *Rheumatol. Int.* 2012, 32, 1397–1401. [CrossRef]

101. Shi, R.; Chen, M.; Litifu, B. Serum interleukin-6 and survivin levels predict clinical response to etanercept treatment in patients with established rheumatoid arthritis. *Mod. Rheumatol.* 2016, 28, 126–132. [CrossRef] [PubMed]

102. Cañete, J.D.; Albala dejo, C.; Hernández, M.V.; Laínez, B.; Pinto, J.A.; Ramírez, J.; López-Armada, M.J.; Rodriguez-Cros, J.R.; Engel, P.; Blanco, F.J.; et al. Clinical significance of high levels of soluble tumour necrosis factor-α receptor-2 produced by alternative splicing in rheumatoid arthritis: A longitudinal prospective cohort study. *Rheumatology* 2011, 50, 721–728. [CrossRef] [PubMed]

103. Kayakabe, K.; Kuroiwa, T.; Sakurai, N.; Ikeuchi, H.; Kadiombo, A.T.; Sakairi, T.; Kaneko, Y.; Maeshima, A.; Hiromura, K.; Nojima, Y. Interleukin-1β measurement in stimulated whole blood cultures is useful to predict response to anti-TNF therapies in rheumatoid arthritis. *Rheumatology* 2012, 51, 1639–1643. [CrossRef]

104. Sakhthiswary, R.; Shaharir, S.S.; Mohd Said, M.S.; Asrul, A.W.; Shahri, N.S. IgA rheumatoid factor as a serological predictor of poor response to tumour necrosis factor α inhibitors in rheumatoid arthritis. *Int. J. Rheum. Dis.* 2014, 17, 872–877. [CrossRef] [PubMed]
Biomedicines 2022, 10, 1808

105. Choi, I.Y.; Gerlag, D.M.; Herenius, M.J.; Thurlings, R.M.; Wijbrandts, C.A.; Foell, D.; Vogl, T.; Roth, J.; Tak, P.P.; Holzinger, D. MRP8/14 serum levels as a strong predictor of response to biological treatments in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* **2015**, *74*, 499–505. [CrossRef]

106. La, D.T.; Collins, C.E.; Yang, H.T.; Migone, T.S.; Stohl, W. B lymphocyte stimulator expression in patients with rheumatoid arthritis treated with tumour necrosis factor alpha antagonists: Differential effects between good and poor clinical responders. *Ann. Rheum. Dis.* **2008**, *67*, 1132–1138. [CrossRef] [PubMed]

107. Odai, T.; Matsunawa, M.; Takahashi, R.; Wakabayashi, K.; Isozaki, T.; Yajima, N.; Miwa, Y.; Kasama, T. Correlation of CX3CL1 and CX3CR1 levels with response to infliximab therapy in patients with rheumatoid arthritis. *J. Rheumatol.* **2009**, *36*, 1158–1165. [CrossRef] [PubMed]

108. Kuuliala, A.; Nissinen, R.; Kautiainen, H.; Repo, H.; Leirisalo-Repo, M. Low circulating soluble interleukin 2 receptor level predicts rapid response in patients with refractory rheumatoid arthritis treated with infliximab. *Ann. Rheum. Dis.* **2006**, *65*, 26–29. [CrossRef] [PubMed]

109. González-Alvaro, I.; Ortiz, A.M.; Tomero, E.G.; Balsa, A.; Orte, J.; Laffon, A.; García-Vicuña, R. Baseline serum RANKL levels may serve to predict remission in rheumatoid arthritis patients treated with TNF antagonists. *Ann. Rheum. Dis.* **2007**, *66*, 1675–1678. [CrossRef] [PubMed]

110. Fabre, S.; Dupuy, A.M.; Dossat, N.; Guisset, C.; Cohen, J.D.; Cristol, J.P.; Daures, J.P.; Jørgensen, C. Protein biochip array technology for cytokine profiling predicts etanercept responsiveness in rheumatoid arthritis. *Clin. Exp. Immunol.* **2008**, *153*, 188–195. [CrossRef] [PubMed]

111. Wijbrandts, C.A.; Dijkgraaf, M.G.; Kraan, M.C.; Vinkenoog, M.; Smeets, T.J.; Dinant, H.; Vos, K.; Lems, W.F.; Wolbink, G.J.; Sijpkens, D.; et al. The clinical response to infliximab in rheumatoid arthritis is in part dependent on pretreatment tumour necrosis factor alpha expression in the synovium. *Ann. Rheum. Dis.* **2008**, *67*, 1139–1144. [CrossRef] [PubMed]

112. Hueber, W.; Tomooka, B.H.; Batiwalla, F.; Li, W.; Monach, P.A.; Tibshirani, R.J.; Van Vollenhoven, R.F.; Lampa, J.; Saito, K.; Tanaka, Y.; et al. Blood autoantibody and cytokine profile predict response to anti-tumor necrosis factor therapy in rheumatoid arthritis. *Arthritis Res. Ther.* **2009**, *11*, R76. [CrossRef] [PubMed]

113. Lindberg, J.; Wijbrandts, C.A.; van Baarsen, L.G.; Nader, G.; Klareskog, L.; Catrina, A.; Thurlings, R.; Vervoordeldonk, M.; Lundeberg, J.; Tak, P.P. The gene expression profile in the synovium as a predictor of the clinical response to infliximab treatment in rheumatoid arthritis. *PLoS ONE* **2010**, *5*, e11310. [CrossRef] [PubMed]

114. Trocmé, C.; Marotte, H.; Baillet, A.; Paillolet-Prades, B.; Garin, J.; Grange, L.; Miossec, P.; Tébèb, J.; Berger, F.; Nissen, M.J.; et al. Apolipoprotein A-I and platelet factor 4 are biomarkers for infliximab response in rheumatoid arthritis. *Ann. Rheum. Dis.* **2009**, *68*, 1328–1333. [CrossRef] [PubMed]

115. Chen, D.Y.; Chen, Y.M.; Chen, H.H.; Hsieh, C.W.; Lin, C.C.; Lan, J.L. Increasing levels of circulating Th17 cells and interleukin-17 predicts rapid response in patients with refractory rheumatoid arthritis treated with infliximab. *Ann. Rheum. Dis.* **2015**, *74*, 1757–1762. [CrossRef] [PubMed]

116. Meusch, U.; Klingner, M.; Baerwald, C.; Rossol, M.; Wagner, U. Deficient spontaneous in vitro apoptosis and increased tmTNF reverse signaling-induced apoptosis of monocytes predict suboptimal therapeutic response of rheumatoid arthritis to TNF inhibition. *Arthritis Res. Ther.* **2013**, *15*, R219. [CrossRef] [PubMed]

117. Obry, A.; Lequerré, T.; Hardouin, J.; Boyer, O.; Fardellone, P.; Philippe, P.; Le Loët, X.; Cosette, P.; Vittecoq, O. Identification of S100A9 as biomarker of responsiveness to the methotrexate/etanercept combination in rheumatoid arthritis using a proteomic approach. *PLoS ONE* **2014**, *9*, e115800. [CrossRef] [PubMed]

118. Blaschke, S.; Rinke, K.; Maring, M.; Flad, T.; Patschan, S.; Jahn, O.; Mueller, C.A.; Mueller, G.A.; Dihazi, H. Haptoglobin-α1, -α2, vitamin D-binding protein and apolipoprotein C-III as predictors of etanercept drug response in rheumatoid arthritis. *Arthritis Res. Ther.* **2015**, *17*, 45. [CrossRef] [PubMed]

119. Zhang, F.; Ding, R.; Li, P.; Ma, C.; Song, D.; Wang, X.; Ma, T.; Bi, L. Interleukin-34 in rheumatoid arthritis: Potential role in clinical therapy. *Int. J. Clin. Exp. Med.* **2015**, *8*, 7809–7815.

120. Meusch, U.; Krasselt, M.; Fattakhova, D.; Baerwald, C.; Klingner, M.; Wagner, U. In vitro response pattern of monocytes after tmTNF reverse signaling predicts response to anti-TNF therapy in rheumatoid arthritis. *J. Transl. Med.* **2015**, *13*, 256. [CrossRef] [PubMed]

121. Obry, A.; Hardouin, J.; Lequerré, T.; Jarnier, F.; Boyer, O.; Fardellone, P.; Philippe, P.; Marcelli, C.; Loët, X.L.; Vittecoq, O.; et al. Identification of 7 Proteins in Sera of RA Patients with Potential to Predict ETA/MTX Treatment Response. *Theranostics* **2015**, *5*, 1214–1224. [CrossRef] [PubMed]

122. Nair, S.C.; Welsing, P.M.; Choi, I.Y.; Roth, J.; Holzinger, D.; Bijlsma, J.W.; van Laar, J.M.; Gerlag, D.M.; Lafeber, F.P.; Tak, P.P. A Personalized Approach Using Clinical Response Based on MRP8/14 Serum Complex Levels in Rheumatoid Arthritis Patients. *PLoS ONE* **2016**, *11*, e0152362. [CrossRef]

123. Ortea, I.; Roschitzki, B.; López-Rodríguez, R.; Tomero, E.G.; Ovalles, J.G.; López-Longo, J.; de la Torre, I.; González-Alvaro, I.; Gómez-Reino, J.J.; González, A. Independent Candidate Serum Protein Biomarkers of Response to Adalimumab and to Infliximab in Rheumatoid Arthritis: An Exploratory Study. *PLoS ONE* **2016**, *11*, e0153140. [CrossRef] [PubMed]

124. Wampler Muskardin, T.; Vashisht, P.; Dorschner, J.M.; Jensen, M.A.; Chrabot, B.S.; Kern, M.; Curtis, J.R.; Danila, M.J.; Cofield, S.S.; Shadick, N.; et al. Increased pretreatment serum IFN-β/α ratio predicts non-response to tumour necrosis factor α inhibition in rheumatoid arthritis. *Ann. Rheum. Dis.* **2016**, *75*, 1757–1762. [CrossRef]
Biomedicines 2022, 10, 1808

125. Koga, T.; Okada, A.; Kawashiri, S.; Kita, J.; Suzuki, T.; Nakashima, Y.; Tamai, M.; Satoh, K.; Origuchi, T.; Iwamoto, N.; et al. Soluble urokinase plasminogen activator receptor as a useful biomarker to predict the response to adalimumab in patients with rheumatoid arthritis in a Japanese population. *Clin. Exp. Rheumatol.* 2011, 29, 811–815. [PubMed]

126. Gerli, R.; Lunardi, C.; Bocci, E.B.; Bobbio-Pallavicini, F.; Schillaci, G.; Caporali, R.; Bistoni, O.; Pirro, M.; Pitzalis, C.; Montecucco, C. Anti-tumor necrosis factor-alpha response in rheumatoid arthritis is associated with an increase in serum soluble CD30. *J. Rheumatol.* 2008, 35, 14–19. [PubMed]

127. Braun-Moscovici, Y.; Markovits, D.; Zinder, O.; Schapira, D.; Rozin, A.; Ehrenburg, M.; Dain, L.; Hoffe, E.; Nahir, A.M.; Balbir-Gurman, A. Anti-cyclic citrullinated protein antibodies as a predictor of response to anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis. *J. Rheumatol.* 2003, 30, 497–500. [PubMed]

128. Nguyen, M.V.C.; Baillet, A.; Romand, X.; Trocmé, C.; Courtier, A.; Marotte, H.; Thomas, T.; Soubrier, M.; Miossec, P.; Tébibi, J.; et al. Prealbumin, platelet factor 4 and S100A12 combination at baseline predicts good response to TNF alpha inhibitors in rheumatoid arthritis. *J. Bone Spine* 2019, 86, 195–201. [CrossRef]

129. Otsubo, H.; Tsuneyoshi, Y.; Nakamura, T.; Matsuda, T.; Komiya, S.; Matsuyama, T. Serum-soluble folate receptor [beta]: A biomarker for the activity of rheumatoid arthritis synovitis and the response to anti-TNF agents. *Clin. Rheumatol.* 2018, 37, 2939–2945. [CrossRef]

130. Frostegård, J.; Ahmed, S.; Hafström, I.; Ajeganova, S.; Rahman, M. Low levels of PCSK9 are associated with remission in patients with rheumatoid arthritis treated with anti-TNF-alpha: Potential underlying mechanisms. *Arthritis Res. Ther.* 2021, 23, 32. [CrossRef] [PubMed]

131. Citro, A.; Scrivo, R.; Martini, H.; Martire, C.; De Marzio, P.; Barna, V.; Valesini, G. CD8+ T Cells Specific to Apoptosis-Associated Antigens Predict the Response to Tumor Necrosis Factor Inhibitor Therapy in Rheumatoid Arthritis. *PLoS ONE* 2015, 10, e0128607. [CrossRef]

132. Hull, D.N.; Cooksley, H.; Chokshi, S.; Williams, R.O.; Abraham, S.; Taylor, P.C. Increase in circulating Th17 cells during anti-TNF therapy is associated with ultrasonographic improvement of synovitis in rheumatoid arthritis. *Arthritis Res. Ther.* 2016, 18, 303. [CrossRef]

133. Plant, D.; Webster, A.; Nair, N.; Oliver, J.; Smith, S.L.; Eyre, S.; Hyyric, K.L.; Wilson, A.G.; Morgan, A.W.; Isaacs, J.D.; et al. Differential Methylation as a Biomarker of Response to Etanercept in Patients with Rheumatoid Arthritis. *Arthritis Rheumatol.* 2016, 68, 1353–1360. [CrossRef] [PubMed]

134. Talotta, R.; Berzi, A.; Atzeni, F.; Batticciotto, A.; Clerici, M.; Sarzi-Puttini, P.; Trabattoni, D. Paradoxical Expansion of Th1 and Th17 Lymphocytes in Rheumatoid Arthritis Following Infliximab Treatment: A Possible Explanation for a Lack of Clinical Response. *J. Clin. Immunol.* 2015, 35, 550–557. [CrossRef] [PubMed]

135. Cuppen, B.V.; Fu, J.; van Wietmarschen, H.A.; Harms, A.C.; van Suijlekom, H.C.; Peeters, J.J.; Bijlsma, J.W.; Tekstra, J.; van Laar, J.M.; et al. Exploring the Inflammatory Metabolomic Profile to Predict Response to TNF-alpha Inhibitors in Rheumatoid Arthritis. *PLoS ONE* 2016, 11, e0163087. [CrossRef]

136. Chara, L.; Sánchez-Atrio, A.; Pérez, A.; Cuende, E.; Albarrán, F.; Turrión, A.; Chevarria, J.; Sánchez, M.A.; Monserrat, J.; de la Hera, A.; et al. Monocyte populations as markers for response to adalimumab plus MTX in rheumatoid arthritis. *Arthritis Res. Ther.* 2012, 14, R175. [CrossRef]

137. Alzabin, S.; Abraham, S.M.; Taher, T.E.; Pallfreeman, A.; Hull, D.; McNamee, K.; Jawad, A.; Pathan, E.; Kinderleier, A.; Taylor, P.C.; et al. Incomplete response of inflammatory arthritis to TNFα blockade is associated with the Th17 pathway. *Ann. Rheum. Dis.* 2012, 71, 1741–1748. [CrossRef]

138. Klaasen, R.; Thurlings, R.M.; Wijbrandts, C.A.; van Kuijik, A.W.; Baeten, D.; Gerlag, D.M.; Tak, P.P. The relationship between synovial lymphocyte aggregates and the clinical response to infliximab in rheumatoid arthritis: A prospective study. *Arthritis Rheum.* 2009, 60, 3217–3224. [CrossRef]

139. Talotta, R.; Berzi, A.; Atzeni, F.; Dell’Acqua, D.; Sarzi Puttini, P.; Trabattoni, D. Evaluation of Th9 lymphocytes in peripheral blood of rheumatoid arthritis patients and correlation with anti-tumor necrosis factor therapy: Results from an in vitro pivotal study. *Reumatismo* 2016, 68, 83–89. [CrossRef]

140. Priori, R.; Casadei, L.; Valerio, M.; Scrivo, R.; Valesini, G.; Manetti, C.; 1H-NMR-Based Metabolomic Study for Identifying Serum Profiles Associated with the Response to Etanercept in Patients with Rheumatoid Arthritis. *PLoS ONE* 2015, 10, e0138537. [CrossRef]

141. Connor, A.M.; Mahomed, N.; Gandhi, R.; Keystone, E.C.; Berger, S.A. TNFα modulates protein degradation pathways in rheumatoid arthritis synovial fibroblasts. *Arthritis Res. Ther.* 2012, 14, R62. [CrossRef]

142. Brun, J. Proteasome inhibition as a novel therapy in treating rheumatoid arthritis. *Med. Hypotheses* 2012, 14, 68–72. [CrossRef]

143. Chitra, S.; Nalini, G.; Rajasekhar, G. The ubiquitin proteasome system and efficacy of proteasome inhibitors in diseases. *Int. J. Rheum. Dis.* 2015, 12, 249–260. [CrossRef]

144. Verbrugge, S.E.; Scheper, R.J.; Lems, W.F.; de Gruijl, T.D.; Jansen, G. Proteasome inhibitors as experimental therapeutics of autoimmune diseases. *Arthritis Res. Ther.* 2015, 17, 17. [CrossRef]

145. Yannaki, E.; Papadopoulou, A.; Anagnostopoulos, A. The proteasome inhibitor bortezomib drastically affects inflammation and bone disease in adjuvant-induced arthritis in rats. *Arthritis Rheumatol.* 2010, 62, 3277–3288. [CrossRef] [PubMed]
146. van der Heijden, J.W.; Oerlemans, R.; Lems, W.F.; Scheper, R.J.; Dijkmans, B.A.; Jansen, G. The proteasome inhibitor bortezomib inhibits the release of NFkappaB-inducible cytokines and induces apoptosis of activated T cells from rheumatoid arthritis patients. *Clin. Exp. Rheumatol.* **2009**, *27*, 92–98.

147. Wang, L.; Liu, L.; Hong, X.; Liu, D.; Cheng, Z. Delanzomib, a Novel Proteasome Inhibitor, Combined with Adalimumab Drastically Ameliorates Collagen-Induced Arthritis in Rats by Improving and Prolonging the Anti-TNF-α Effect of Adalimumab. *Front. Pharmacol.* **2021**, *12*, 782385. [CrossRef]

148. Liu, J.; Li, J.; Chen, M.; Kuang, L. Bortezomib followed by autologous stem cell transplantation in a patient with rheumatoid arthritis: A case report and review of the literature. *Medicine* **2016**, *95*, e5760. [CrossRef]

149. Pascart, T.; Herbaux, C.; Lemaire, A.; Soncin, F.; Hachulla, E.; Hatron, P.Y.; Terriou, L. Coexistence of rheumatoid arthritis and TEMPI syndrome: New insight in microangiogenic-related diseases. *Jt. Bone Spine* **2016**, *83*, 587–588. [CrossRef]

150. Sandoo, A.; van Zanten, J.J.; Toms, T.E.; Carroll, D.; Kitas, G.D. Anti-TNFα therapy transiently improves high density lipoprotein cholesterol levels and microvascular endothelial function in patients with rheumatoid arthritis: A pilot study. *BMC Musculoskelet. Disord.* **2012**, *13*, 127. [CrossRef] [PubMed]

151. Seriolo, B.; Paolino, S.; Sulli, A.; Fasciolo, D.; Cutolo, M. Effects of anti-TNF-alpha treatment on lipid profile in patients with active rheumatoid arthritis. *Ann. N. Y. Acad. Sci.* **2006**, *1069*, 414–419. [CrossRef] [PubMed]

152. Hassan, S.; Milman, U.; Feld, J.; Eder, L.; Lavi, I.; Cohen, S.; Zisman, D. Effects of anti-TNF-α treatment on lipid profile in rheumatic diseases: An analytical cohort study. *Arthritis Res. Ther.* **2016**, *18*, 261. [CrossRef]

153. Cacciapaglia, F.; Anelli, M.G.; Rinaldi, A.; Serafini, L.; Covelli, M.; Scioscia, C.; Iannone, F.; Lapadula, G. Lipid profile of rheumatoid arthritis patients treated with anti-tumor necrosis factor-alpha drugs changes according to disease activity and predicts clinical response. *Drug Dev. Res.* **2014**, *75* (Suppl. S1), S77–S80. [CrossRef]

154. Dong, H.; Liu, F.; Ma, F.; Xu, L.; Pang, L.; Li, X.; Liu, B.; Wang, L. Montelukast inhibits inflammatory response in rheumatoid arthritis fibroblast-like synoviocytes. *Int. Immunopharmacol.* **2018**, *61*, 215–221. [CrossRef] [PubMed]

155. Iwasaki, T.; Watanabe, R.; Ito, H.; Fujii, T.; Okuma, K.; Oku, T.; Hirayama, Y.; Ohmura, K.; Murata, K.; Murakami, K.; et al. Dynamics of Type I and Type II Interferon Signature Determines Responsiveness to Anti-TNF Therapy in Rheumatoid Arthritis. *Front. Immunol.* **2022**, *13*, 901437. [CrossRef] [PubMed]

156. Aldridge, J.; Lundell, A.C.; Andersson, K.; Mark, L.; Lund Hetland, M.; Østergaard, M.; Uhlig, T.; Schrumpf Heiberg, M.; Haavardsholm, E.A.; Nurmohamed, M.; et al. Blood chemokine levels are markers of disease activity but not predictors of remission in early rheumatoid arthritis. *Clin. Exp. Rheumatol.* **2022**, *40*, 1393–1402. [CrossRef] [PubMed]