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REVIEW

Cytokines Focus

Interleukin-17 in rheumatoid arthritis: Trials and tribulations

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Interleukin-17A (IL-17A) is a pro-inflammatory cytokine with well-characterized biological effects on stromal cell activation, angiogenesis, and osteoclastogenesis. The presence of this cytokine in the inflamed joints of patients with rheumatoid arthritis (RA), together with compelling data from in vitro and experimental arthritis models demonstrating its pro-inflammatory effects, made this cytokine a strong candidate for therapeutic targeting. Clinical trials, however, have shown relatively modest success in RA as compared with other indications. Guided by recent insights in IL-17 biology, this review aims to explore possible reasons for the limited clinical efficacy of IL-17A blockade in RA, and what we can learn from these results going forward.

Introduction

IL-17 is a term used to refer to either the single cytokine IL-17A or the IL-17 family of cytokines, which consists of IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F. IL-17A was the first characterized member of the IL-17 family, and to date is still the most studied member.

IL-17A was first identified by Rouvier et al. in 1993; they cloned a rodent cDNA sequence, termed *CTLA8*, from an activated T cell hybridoma using a subtractive hybridization approach (Rouvier et al., 1993). The predicted amino acid sequence of *CTLA8* was found to be 57% homologous to the predicted amino acid sequence of ORF13 of *Herpesvirus saimiri*. In 1995, Yao et al. termed the protein product of murine CTLA8 IL-17, and cloned its receptor IL-17R (now known as IL-17RA). They demonstrated that IL-17 exhibited classic pleiotropic activities including NF-κB activation and IL-6 production by mouse fibroblasts (Yao et al., 1995a). The same group cloned human IL-17 and showed that this cytokine was predominantly produced by activated $CD4^+$ T cells, although low-level production by $CD8^+$ T cells was consistently observed (Yao et al., 1995b).

The potential biological relevance of IL-17A in inflammatory arthritis became clear when Miossec and co-workers demonstrated the presence of IL-17A in synovial tissue from patients with rheumatoid arthritis (RA; Chabaud et al., 1999). These findings indicated a potential inflammatory role of IL-17A in the immunopathology of RA. This concept was rapidly supported in vivo by various experimental models of arthritis, and through several human in vitro experiments (reviewed in van den Berg and Miossec, 2009). As a result, it was not long before clinical trials aimed at IL-17A blockade in RA were conducted. Unexpectedly, despite the strong evidence from the experimental models and the human in vitro and in situ data, the clinical efficacy of IL-17A blockade in RA is relatively modest. As a result, in the United Kingdom, IL-17A blockade has not been recommended as a treatment for RA by the National Institute for Health and Care Excellence. In contrast, IL-17A blockade has shown great clinical success in psoriasis, with recent studies also showing robust clinical efficacy in ankylosing spondylitis and psoriatic arthritis (PsA), leading to National Institute for Health and Care Excellence approval for these indications.

In this review, I will summarize the key findings that highlighted IL-17A as a therapeutic target in RA, discuss the current knowledge regarding other IL-17 family members in RA, and summarize the clinical trial findings. I will then explore possible reasons for the limited clinical success of IL-17A blockade in RA guided by recent insights from IL-17 biology research.

Identification of IL-17A as a therapeutic target in RA

IL-17A in RA

The identification of IL-17A–producing T cells in the RA synovium (Chabaud et al., 1999) and the subsequent demonstration of the degrading effects of IL-17A on RA bone explants (Chabaud

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et al., 2001a) firmly placed IL-17 as a potential therapeutic target in this disease. A large number of experimental animal studies showed that inhibition of IL-17A signaling, through treatment with an IL-17R fusion protein or IL-17A neutralizing antibodies or using IL-17R–deficient animals, reduced disease in adjuvant arthritis (Bush et al., 2002), collagen-induced arthritis (CIA; Lubberts et al., 2004), antigen-induced arthritis (Koenders et al., 2005b), and streptococcal cell wall–induced arthritis (Koenders et al., 2005a). Conversely, intra-articular injection of adenoviral vectors expressing IL-17A was sufficient to boost arthritis in collagen-induced arthritis or streptococcal cell wall–induced arthritis (Koenders et al., 2005c; Lubberts et al., 2002).

In vitro human model systems further underpinned these compelling in vivo data by demonstrating the pleiotropic effects of IL-17A: the addition of hrIL-17A resulted in increased IL-6, IL-8, CCL2, CXCL1, vascular endothelial growth factor, and matrix metalloproteinase-1 production by RA synoviocytes (Chabaud et al., 1998, 1999, 2000; Fossiez et al., 1996; Ota et al., 2015; Ryu et al., 2006); increased IL-1β, TNF, and CCL20 production by human monocytes or macrophages (Chabaud et al., 2001b; Matsumoto and Kanmatsuse, 2003); and enhanced osteoclastogenesis (Kim et al., 2015; Yago et al., 2009) and angiogenesis (Pickens et al., 2010).

The identification of a specific lineage of IL-17A–producing CD4$^+$ T cells, called T helper (Th) 17 cells (Langrish et al., 2005; Veldhoen et al., 2006), further stimulated this area of research. Several studies have documented the increased presence of IL-17A and/or Th17 cells in the blood and inflamed joints of patients with RA (Gullick et al., 2010; 2013; Kirkham et al., 2006; Leipe et al., 2010; Shen et al., 2009), and in some cases have shown an association with disease activity or joint damage progression (Gullick et al., 2010; Kirkham et al., 2006; Leipe et al., 2010).

Other IL-17 family members in RA

IL-17A is a member of a larger family of cytokines, consisting of IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F (recently reviewed by McGeachy et al., 2019). While most attention has been focused on the pro-inflammatory nature of IL-17A, a potential role in inflammation of the other IL-17 family members is emerging.

An early study in mice showed that in addition to *Il17a*, mRNA for *Il17b*, *Il17c*, and *Il17f* was detected in arthritic paws in CIA mice. Adoptive transfer of CD4$^+$ T cells retrovirally transduced with the mIL-17A, B, C, or F genes all exacerbated CIA, suggesting a role for these cytokines at least in this experimental model (Yamaguchi et al., 2007). The same study also showed that neutralization of IL-17B ameliorated disease. Relatively little is known regarding the role in RA of IL-17B, which has 29% homology with IL-17A (Bie et al., 2017). One study showed that IL-17B mRNA and protein is expressed in RA synovial tissue, where it is produced by neutrophils. IL-17B and TNF were also shown to synergistically induce production of IL-6 and G-CSF by fibroblasts (Kouri et al., 2014). IL-17B can also induce increased production of TNF and IL-1β in the monocytic cell line THP-1 (Li et al., 2000), but how this relates to primary monocytes in RA is not yet known.

IL-17C (23% homology with IL-17A) is preferentially produced by epithelial cells. It is predominantly involved in regulation of epithelial function due to the expression of IL-17RE on epithelial cells, which combines with IL-17RA to make a functional IL-17C receptor (Pappu et al., 2012). IL-17RE expression is also upregulated on Th17 cells, as well as on γδ T cells, at least in mice (Chang et al., 2011). This may have functional consequences, as *Il17c*$^{-/-}$ mice showed a reduction in Th17 cell–mediated experimental autoimmune encephalomyelitis (EAE) compared with control mice. IL-17C has been shown to have a role in experimental arthritis (Yamaguchi et al., 2007) and certain T cell–independent inflammatory disease models in mice (Yamaguchi et al., 2018). However, it should be noted that the adoptive transfer of T cells retrovirally transduced with IL-17C as used in the experimental arthritis model (Yamaguchi et al., 2007) is rather artificial, and only allows a suggestion that IL-17C may exacerbate joint inflammation. As yet, very little is known about the presence and possible function of IL-17C in human RA.

IL-17D (25% homology with IL-17A) is the most enigmatic cytokine of the IL-17 family. It was cloned in 2002 and shown to be expressed highly in skeletal muscle, brain, adipose tissue, heart, lung, and pancreas, with some expression also by resting CD4$^+$ T cells (Starnes et al., 2002). IL-17D increased expression of IL-6, IL-8, and GM-CSF by HUVEC cells but had an inhibitory effect on myeloid progenitor cell proliferation. Recent studies indicate that IL-17D expression is regulated by the transcription factor nuclear factor erythroid-derived 2-like 2, a known sensor for oxidative and xenobiotic stress, and that IL-17D deficiency may predispose animals to cancer and viral infection (Saddawi-Konefka et al., 2016). Thus far, no studies have investigated the potential contribution of IL-17D to RA.

IL-17E has the least homology with IL-17A (17%) and is also known as IL-25. It is mostly studied in the context of Th2 cell responses as it induces the production of IL-4, IL-5, and IL-13, thereby protecting the host against parasitic infections while contributing to the development of allergic disease. Interestingly, IL-17E was found to protect mice from EAE by suppressing Th17 cells (Kleinschek et al., 2007) and to inhibit IL-17A, IFN-γ, and TNF production by stimulated CD4$^+$ T cells from patients with inflammatory bowel disease while promoting IL-10 production (Su et al., 2013). IL-17E levels were shown to be increased in the serum and synovial fluid of patients with RA, and to correlate with clinical parameters of disease (Liu et al., 2016). Furthermore, addition of recombinant IL-17E suppressed human and mouse Th17 cell responses and attenuated CIA in mice (Liu et al., 2016). IL-17E/IL-25 may thus contribute to limiting inflammation in RA.

IL-17F has the highest homology with IL-17A (~50%). It has a similar but less potent inflammatory function as IL-17A, although nonredundant functions have been reported in mouse models (Yang et al., 2008). The presence of IL-17F in RA is still debated. Some studies show the presence of IL-17F in RA plasma or synovial fluid (Jain et al., 2015), and of IL-17F–producing cells in RA synovial tissue (Zrioual et al., 2009), albeit at highly variable levels (van Baarsen et al., 2014). Other studies did not detect IL-17F protein in culture supernatants from PMA/ionomycin-stimulated synovial fluid mononuclear cells (SFMC) from patients with RA (Sarkar et al., 2014). We recently investigated the presence of IL-17F and IL-17F–producing cells in the

RA joint but did not detect IL-17F levels in the synovial fluid, nor IL-17F–expressing CD4+ T cells in SFMC ex vivo. IL-17F–producing CD4+ T cells were, however, readily detected upon in vitro stimulation of SFMC, suggesting that cells with IL-17F–producing potential exist in the inflamed joint (Burns et al., 2019). We also found that IL-17F synergizes with TNF to potently induce IL-6 and IL-8 by RA synovial fibroblasts, in support of previous work (Zrioual et al., 2009). While further research certainly still is required, the existing data suggest a potential role for IL-17F in RA.

IL-17A blockade in RA

Clinical trials aimed at targeting IL-17A

The compelling evidence for the pro-inflammatory nature of IL-17A and its presence in the inflamed RA joint led to several clinical trials aimed at investigating the therapeutic effect of IL-17A inhibition in RA. The first phase I studies on the effects of IL-17A blockade were published in 2010. In one trial, 26 patients were treated with two infusions of 10 mg/kg AIN457 (now known as secukinumab). American College of Rheumatology (ACR) 20% (ACR20) response rates at week 6 (primary endpoint) were higher in AIN457-treated patients than placebo (47% vs. 27%, P = 0.12; treatment difference was a priori considered statistically significant if P < 0.2; Hueber et al., 2010). In the other trial, a total of 77 patients with RA were treated with escalating doses of LY2439821 (now known as ixekizumab). Significantly greater percentages of patients achieved ACR20 or ACR50 responses upon treatment with LY2439821 compared with placebo (Genovese et al., 2010).

Two phase II placebo-controlled studies with secukinumab have been conducted in patients with RA with inadequate response to methotrexate. In both studies, the primary efficacy endpoints, predefined as percentage of ACR20 responders at week 16 (Genovese et al., 2013) or week 12 (Tlustochowicz et al., 2016), were not met. Significant changes in some secondary endpoints including disease activity score in 28 joints (DAS28) were observed. A 1-yr follow-up study of the former study revealed that patients with improved responses at week 16 sustained these responses through to week 52, with the greatest improvement seen in patients receiving 150 mg, although this was not placebo-controlled at this stage (Genovese et al., 2014a). A further randomized study of biological-naive subjects with tender/swollen joint (each six or more) counts and high-sensitivity C-reactive protein (CRP; >10 mg/liter) showed that secukinumab was significantly more effective than placebo in reducing DAS28-CRP and producing ACR20 and ACR50 responses at week 12 (Burmester et al., 2016). A phase II randomized placebo-controlled study of subcutaneous ixekizumab in 260 biological-naive patients with RA or 188 patients with inadequate response to TNF inhibitors showed significant ACR20 responses at week 12 (Genovese et al., 2014b). In contrast, a recent phase II study with a fully human anti–IL-17A mAb (CNTO6785) in patients with RA with inadequate response to methotrexate did not demonstrate clinical efficacy (Mease et al., 2018).

Two phase III studies with secukinumab showed a significant increase in ACR20 responses compared with placebo at week 24 in patients with active RA who had an inadequate response to or intolerance of TNF inhibitors (Blanco et al., 2017; Tahir et al., 2017). No incremental benefit was observed as compared with treatment with abatacept (CTLA-4-Ig; Blanco et al., 2017). A third phase III study in TNF nonresponders reported that ACR20 response rates at week 24 were not statistically superior to placebo (Dokoupilová et al., 2018).

These collective data indicate that while there is clinical efficacy of IL-17A blockade compared with placebo in patients with RA (Kunwar et al., 2016), effects (mostly measured as ACR20 responses) are relatively modest. Some of these trials were conducted in patients who were anti-TNF nonresponders, and consideration should be given to the possibility that it may be more challenging to achieve clinical efficacy in this patient group.

More recently, dual blockade of IL-17A and TNF has been investigated using ABT-122, a dual variable domain Ig that targets human TNF and IL-17A (Fleischmann et al., 2017). A phase II study demonstrated that while dual inhibition of IL-17A and TNF was clinically efficacious, there was no meaningful difference in the ACR20 response at week 12 compared with treatment with anti-TNF (adalimumab) alone (Genovese et al., 2018). A recent phase IIa proof-of-concept study tested dual blockade of IL-17A and IL-17F using bimekizumab as add-on treatment in patients with RA who had an inadequate response to TNF. A greater reduction in DAS28-CRP at week 20 (primary endpoint) was observed in the anti-TNF inadequate response plus bimekizumab group compared with the anti-TNF inadequate response plus placebo group (Glatt et al., 2019).

Finally, studies have also investigated IL-17RA blockade in RA using brodalumab. IL-17RA is part of the receptor for IL-17A, IL-17F, IL-17C, and IL-17E, and thus, IL-17RA blockade may affect signaling from all these cytokines (Gaffen, 2009). However, in RA, no clinical efficacy of IL-17RA blockade was observed (Martin et al., 2013; Pavelka et al., 2015).

Possible reasons for the limited clinical success of IL-17A blockade in RA

A key question emerges: Why was IL-17A blockade not as successful in RA as could reasonably be expected from experimental and in vitro models? Several nonmutually exclusive reasons may underlie its limited success.

First, we should consider the possibility that IL-17A is not involved at all in the pathogenesis of RA. However, as highlighted at the beginning of this review, the presence of IL-17A in the RA joint and its clear in vitro effects on pro-inflammatory cytokine production, angiogenesis, and osteoclastogenesis strongly suggest that IL-17A at least contributes to the overall inflammatory milieu that is present in the RA joint. It should be noted, though, that IL-17A expression in patients with RA is heterogeneous, and not all patients exhibit high IL-17A levels or Th17 cell frequencies (Gullick et al., 2010; Kirkham et al., 2006; Leipe et al., 2010; van Baarsen et al., 2014). It has been shown that IL-17A expression in the joint correlates with serum CRP levels (Gullick et al., 2010; Kirkham et al., 2006), and in this context, it is interesting that one of the phase II secukinumab studies reported better responses in patients with elevated CRP levels above 10 mg/liter (Burmester et al., 2016). The same study

also explored whether secukinumab was more clinically efficacious in patients with RA who carried the *HLA-DRB1*04* allele (the most commonly associated HLA-DR allele with RA) or the *HLA-DRB1*SE* (shared epitope). The shared epitope, a five–amino acid sequence motif in residues 70–74 of the DRβ chain encoded by several *HLA-DRB1* alleles, is a genetic risk factor for RA and has been suggested to induce Th17 cell polarization (De Almeida et al., 2010). However, no meaningful association was observed between HLA-DRB1 carrier status and DAS28-CRP or ACR20 response at week 12 to secukinumab relative to placebo (Burmester et al., 2016). None of the clinical trials performed thus far stratified patients based on IL-17A/Th17 cell or CRP levels, and thus it cannot be ruled out that stronger clinical efficacy may have been observed with a precision medicine approach.

It is also possible that IL-17A blockade alone is not sufficient to effectively disrupt inflammatory signals. While IL-17A signaling has a proinflammatory effect, it is not as potent as TNF. Thus, neutralizing IL-17A only will not block the continuing proinflammatory effects of TNF. Furthermore, as noted above, IL-17A, IL-17B, and IL-17F can all synergize with TNF. Hence, upon neutralization of IL-17A alone, the synergistic effects of IL-17F, and possibly IL-17B, with TNF can still induce potent inflammatory effects. Results from clinical trials with dual blocking antibodies such as ABT-122 (blocking IL-17A and TNF) or bimekizumab (targeting the combination of IL-17A/IL-17F) will be of interest in this regard.

A third consideration is that IL-17A may play distinct or differential roles in early versus late disease. It has been shown in mouse models of EAE that Th17 cells are induced early in the disease process and that these cells, through expression of CCR6, can migrate into the uninflamed central nervous system (Reboldi et al., 2009; Ronchi et al., 2016). This first wave of migratory T cells is required for the recruitment of a second wave of T cells, including Th1 and Th17 cells, which then culminates in full immunopathology. It has also been shown in the same experimental model that Th17 cells can lose their IL-17A expression and "convert" into IFN-γ–only producing T cells during the disease course (Hirota et al., 2011). Evidence from experimental arthritis models suggests that while Th17 cells may be present even before onset of disease, IL-17A may play a more prominent role in the erosive stages of disease (Joosten et al., 2008; Koenders et al., 2005b). These findings suggest that IL-17A–producing T cells may not be consistently present throughout the disease course, and that IL-17A blockade may be more efficacious in certain subsets of patients, for example, those with early RA or patients with aggressively erosive disease. Temporal effects of cytokine function are generally not considered in clinical trial design, and this again may have influenced the trial outcomes.

It is also well-established that not all Th17 cells are pathogenic, and that IL-10–producing nonpathogenic Th17 cells exist (Lee et al., 2012; Zielinski et al., 2012). Our own work showed that increased frequencies of IL-10–producing Th17 cells are observed upon TNF blockade in vitro and in patients with RA in vivo (Evans et al., 2014; Roberts et al., 2017). It will be important to establish if and how IL-17A blockade affects the induction or function of these IL-10–producing Th17 cells.

Finally, in recent years, a vast body of evidence has shown that IL-17A is not solely produced by $CD4^+$ T cells but can also be produced by other cellular sources including $CD8^+$ T cells, γδ T cells, mucosa-associated invariant T cells, and innate lymphoid cells. We have shown that while IL-17A–producing $CD8^+$ T cells are not enriched in the inflamed joints of patients with RA, they are present at increased frequencies in the joints of patients with PsA and spondyloarthritis (Menon et al., 2014; Steel et al., 2019). IL-17A–producing $CD8^+$ T cells have also been described in the inflamed skin lesions of patients with psoriasis (Res et al., 2010). PsA, spondyloarthritis, and psoriasis are HLA class I–associated diseases, suggesting a role for $CD8^+$ T cells, while RA has a strong HLA class II association, implying a role for $CD4^+$ T cells. Psoriasis and spondyloarthritides also have various genetic associations with the IL-17/IL-23 pathway and show good clinical responses to IL-17A blockade (reviewed in Taams et al., 2018). This brings forward the fascinating question whether the cellular source of IL-17A may be relevant to the clinical success of IL-17A inhibition. While it is difficult to envision how neutralization of secreted IL-17A would be affected by the cellular source of the cytokine, it is possible that positive pro-inflammatory feedback loops between specific IL-17A–producing cells and IL-17RA/RC–bearing target cells could be affected differentially by IL-17A inhibition. Furthermore, different cellular sources may have different epigenetic regulation of *IL17A* expression, resulting in altered or longer-term stability, or coexpress different inflammatory mediators that influence the downstream effects of IL-17A. Finally, evidence is accumulating of IL-23–independent IL-17 production (Cuthbert et al., 2019), which supports the notion that not all IL-17–producing cell subsets are the same. Determining the presence and pathogenic role of different cellular sources of IL-17 in inflammatory arthritis will help clarify how IL-17 blockade might exert its effects.

Concluding remarks

The identification of IL-17A and IL-17A–producing $CD4^+$ T cells in the rheumatoid joint together with the biological function of IL-17A in promoting inflammation, angiogenesis, and osteoclastogenesis made this cytokine a prime candidate for therapeutic targeting in RA. Clinical trials directed at IL-17A blockade, however, have shown mostly modest effects in RA, especially as compared with the clinical efficacy observed in psoriasis, PsA, and spondyloarthritis. While the limited clinical success in RA may understandably prompt pharmaceutical industries to focus their efforts on those indications in which the strongest clinical response is demonstrated, one should take care not to throw out the baby with the bathwater. As highlighted here, there are some plausible potential reasons for the limited clinical success of IL-17A blockade in RA. Using this knowledge together with our growing understanding of precision medicine, it may be possible, perhaps even prudent, to design investigator-led trials to assess the effect of IL-17A blockade in specific groups of patients with RA, e.g., those with high levels of IL-17A or Th17 cells in synovial fluid/tissue, those with rapidly progressing erosive disease, or those with early RA and high CRP. Testing newly emerging drugs such as dual cytokine blockade of IL-17A/TNF or IL-17A/IL-17F, again in stratified patient groups, may be an

additional avenue to pursue. While these approaches may not provide added value for the majority of patients with RA over and above the existing treatment options, they may benefit those patients for whom current therapies are not sufficient.

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